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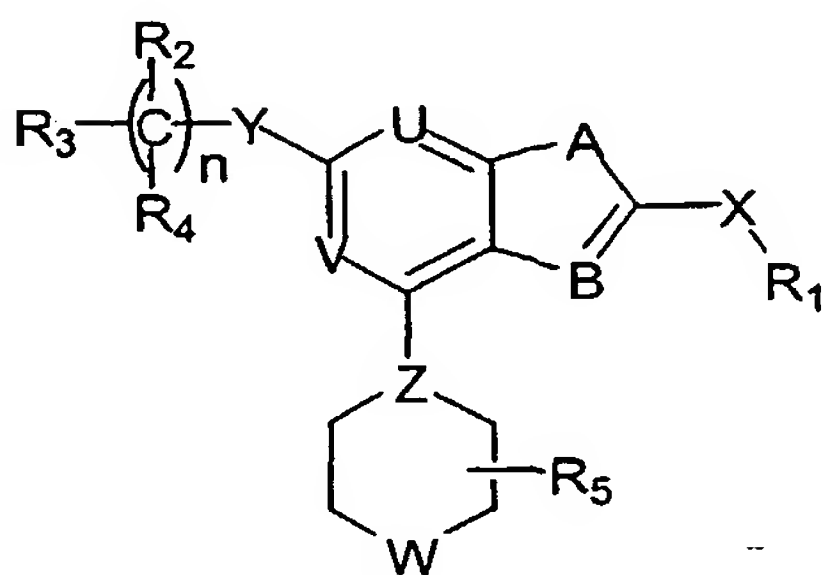
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(I).

aryl, heteroaryl, cyclyl, or heterocyclyl; R^c is H, alkyl, aryl, acyl, or sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxyl, amino, ester, amide, CN, or halogen. The compound is useful for treating an interleukin-12 overproduction-related disorder.

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NOVEL COMPOUNDS

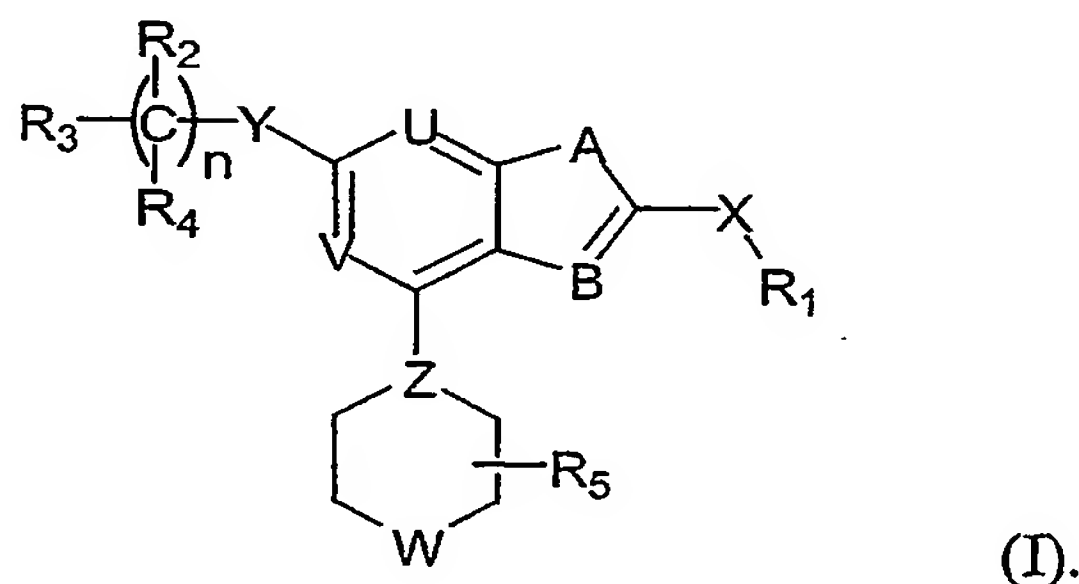
BACKGROUND

Interleukin-12 (IL-12) is a heterodimeric cytokine (p70) composed of two subunits (p35 and p40), and plays key roles in immune responses by bridging innate resistance and antigen-specific adaptive immunity. Trinchieri (1993) *Immunol Today* 14: 335. For example, it promotes type 1 T helper cell (Th1) responses and, hence, cell-mediated immunity. Chan *et al.* (1991) *J Exp Med* 173: 869; Seder *et al.* (1993) *Proc Natl Acad Sci USA* 90: 10188; Manetti *et al.* (1993) *J Exp Med* 177: 1199; and Hsieh *et al.* (1993) *Science* 260: 547. Overproduction of IL-12 causes excessive Th1 responses, and may result in inflammatory disorders, such as insulin-dependent diabetes mellitus, multiple sclerosis, rheumatoid arthritis, psoriasis, Crohn's disease, or sepsis. See, e.g., Gately *et al.* (1998) *Annu Rev Immunol.* 16: 495; and Abbas *et al.* (1996) *Nature* 383: 787. Thus, inhibiting IL-12 overproduction is an approach to treat the just-mentioned diseases. Trembleau *et al.* (1995) *Immunol. Today* 16: 383; and Adorini *et al.* (1997) *Chem. Immunol.* 68: 175. For example, overproduction of IL-12 and the resultant excessive Th1 type responses can be suppressed by modulating IL-12 production. A compound that down-regulates IL-12 production can be used for treating inflammatory diseases. Ma *et al.* (1998) *Eur Cytokine Netw* 9: 54.

SUMMARY

The present invention is based, in part, on the discovery of novel compounds, which are capable of modulating IL-12 production.

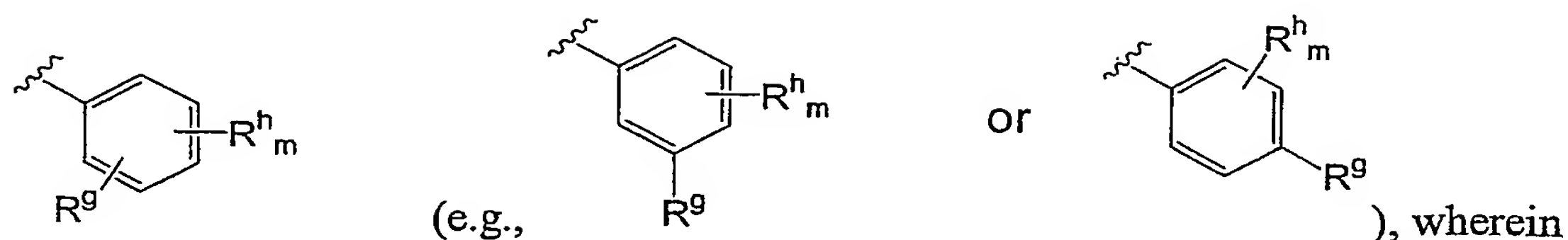
In one aspect, this invention features a compound of formula (I) that contains an aromatic bicyclic ring:



R_1 is aryl or heteroaryl; each of R_2 and R_4 , independently, is H, halogen, CN, alkyl, OR^a , or NR^aR^b ; R_3 is H, halogen, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$, $NR^aC(NR^b)NR^cR^d$, $NR^aC(O)OR^b$, $S(O)NR^aR^b$, $S(O)_2NR^aR^b$, $S(O)R^a$, $S(O)_2R^a$, $C(O)R^a$, $C(O)OR^a$, or $C(O)NR^aR^b$; R_5 is H or alkyl; n is 0, 1, 2, 3, 4, 5, or 6; A is O, S, $S(O)$, $S(O)_2$, or NR^e ; B is N or CR^f ; X is O, S, $S(O)$, $S(O)_2$, NR^e , or $C(O)$; Y is a covalent bond, $C(O)$, $C=NR^a$, O, S, $S(O)$, $S(O)_2$, or NR^e ; Z is N or CH; each of U and V , independently, is N or CR; and W is O, S, or NR^e ; in which each of R^a , R^b , R^c , and R^d , independently, is H, alkyl, aryl, heteroaryl, cyclyl, or heterocyclyl; R^e is H, alkyl, aryl, acyl, or sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxyl, amino, ester, amide, CN, or halogen; and provided that if each of U and V is N, Y is a covalent bond, n is 0, then R_3 is H, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$, $NR^aC(NR^b)NR^cR^d$, $NR^aC(O)OR^b$, $S(O)NR^aR^b$, $S(O)_2NR^aR^b$, $S(O)R^a$, $S(O)_2R^a$, $C(O)R^a$, $C(O)OR^a$, or $C(O)NR^aR^b$. Note that the left atom shown in any substituted group described above is closest to the aromatic bicyclic ring. Also note that when there are more than one R^a -containing substituted groups in a compound of formula (I), the R^a moieties can be the same or different. The same rule applies to other similar situations.

Referring to the just-described compounds, a subset of these compounds is featured by that A is NR^e , and B is N. Another subset of the compounds are those wherein Z is N and W is O; or X is NR^e .

Further another subset of the compounds are those wherein each of U and V is N. In these compounds, A can be NR^e , B can be N, Y can be NR^e or O, Z can be N, W can be O, R_1 can be aryl, and R_3 can be halogen, CN, alkyl, aryl, heteroaryl, OR^a , $OC(O)R^a$, NR^aNR^b , $NR^aC(O)R^b$, $C(O)OR^a$, or $C(O)NR^aR^b$. In some embodiments, R_3 is aryl, heteroaryl (e.g., pyridinyl, triazolyl, tetrazolyl, pyrimidinyl, thiazolyl, indolyl, or indolizinyl), aryloxy, or heteroaryloxy. In some other embodiments, R_1 is



R^g is H, halogen, CN, alkyl, or alkoxy; R^h is halogen (F, Cl, Br, or I), CN, hydroxyl, amino, alkyl (e.g., Me, Et, Pr, or *i*-Pr), aryl, heteroaryl, alkoxy (e.g., OMe or OEt), aryloxy, heteroaryloxy, acyl (e.g., C(O)CH₃), alkoxycarbonyl (e.g., C(O)OCH₃), alkylcarbonoxyl (e.g., OC(O)CH₃), mono- or dialkylaminocarbonyl (e.g., NC(O(CH₃)₂)), amidinyl (e.g., C(NH)NH₂), ureayl (e.g., NHC(O)NH₂), guanadiny (e.g., NHC(NH)NH₂), sulfonyl (e.g., SO₂CH₃), or sufonamidyl (e.g., SO₂NH₂); and *m* is 0, 1, 2, 3, or 4.

Alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, and heterocyclyl mentioned above include both substituted and unsubstituted moieties. The term "substituted" refers to one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of substituents include, but are not limited to, halogen, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, carbonyl, carbamido, carbamyl, carboxyl, thioureido, thiocyanato, sulfoamido, C₁~C₆ alkyl, C₁~C₆ alkenyl, C₁~C₆ alkoxy, aryl, heteroaryl, cyclyl, heterocyclyl, wherein alkyl, alkenyl, alkoxy, aryl, heteroaryl cyclyl, and heterocyclyl are optionally substituted with C₁~C₆ alkyl, aryl, heteroaryl, halogen, hydroxyl, amino, mercapto, cyano, or nitro.

As used herein, the term "alkyl" refers to a straight-chained or branched alkyl group containing 1 to 6 carbon atoms. Examples of alkyl groups include methyl (Me), ethyl (Et), *n*-propyl (Pr), isopropyl (*i*-Pr), *tert*-butyl, and *n*-pentyl.

The term "alkenyl" refers to a straight-chained or branched alkenyl group containing 2 to 6 carbon atoms. Examples of alkenyl groups include vinyl, allyl (2-propenyl), dimethylallyl, and butenyl.

The term "alkynyl" refers to a straight-chained or branched alkynyl group containing 2 to 6 carbon atoms. Examples of alkynyl groups include ethynyl and propargyl.

The term "aryl" refers to a hydrocarbon ring system (monocyclic or bicyclic) having at least one aromatic ring. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, and pyrenyl.

The term "heteroaryl" refers to a hydrocarbon ring system (monocyclic or bicyclic) having at least one aromatic ring which contains at least one heteroatom (e.g., O, N, or S) as part of the ring system. Examples of heteroaryl moieties include, but are not limited to, pyridinyl, triazolyl, tetrazolyl, pyrimidinyl, thiazolyl, indolyl, and indoliziny.

The terms "cyclyl" and "heterocyclyl" refer to partially and fully saturated mono- or bi-cyclic rings having from 4 to 14 ring atoms. A heterocyclyl ring contains one or more heteroatoms (e.g., O, N, or S) as part of the ring. Exemplary cyclyl and heterocyclyl rings are cyclohexane, piperidine, piperazine, morpholine, thiomorpholine, and 1,4-oxazepane.

In another aspect, this invention features a pharmaceutical composition that contains a pharmaceutically acceptable carrier and an effective amount of at least one of the aforementioned compounds.

In further another aspect, the present invention features a method for treating an IL-12 overproduction-related disorder (e.g., rheumatoid arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or insulin-dependent diabetes mellitus). The method includes administering to a subject in need thereof an effective amount of a compound of formula (I), wherein R_1 is aryl or heteroaryl; each of R_2 and R_4 , independently, is H, halogen, CN, alkyl, OR^a , or NR^aR^b ; R_3 is H, halogen, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$, $NR^aC(NR^b)NR^cR^d$, $NR^aC(O)OR^b$, $S(O)NR^aR^b$, $S(O)_2NR^aR^b$, $S(O)R^a$, $S(O)_2R^a$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^b$; R_5 is H or alkyl; n is 0, 1, 2, 3, 4, 5, or 6; A is O, S, $S(O)$, $S(O)_2$, or NR^e ; B is N or CR^f ; X is O, S, $S(O)$, $S(O)_2$, NR^e , or $C(O)$; Y is a covalent bond, $C(O)$, $C=NR^a$, O, S, $S(O)$, $S(O)_2$, or NR^e ; Z is N or CH; each of U and V , independently, is N or CR; and W is O, S, or NR^e ; in which each of R^a , R^b , R^c , and R^d , independently, is H, alkyl, aryl, heteroaryl, cyclyl, or heterocyclyl; R^e is H, alkyl, aryl, acyl, or sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxyl, amino, ester, amide, CN, or halogen.

The structures of 55 above-described compounds are shown in Examples 1-55 below.

The compounds described above include the compounds themselves, as well as their salts and their prodrugs, if applicable. Such salts, for example, can be formed between a positively charged substituent (e.g., amino) on a compound and an anion. Suitable anions include, but are not limited to, chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a negatively charged substituent (e.g., carboxylate) on a compound can form a salt with a cation. Suitable cations include, but are not limited to, sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing the compounds described above.

In addition, some of the compounds have one or more double bonds, or one or more asymmetric centers. Such compounds can occur as racemates, tautomers, racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- or *E*- or *Z*- double isomeric forms.

Further, the aforementioned compounds also include their *N*-oxides. The term "*N*-oxides" refers to one or more nitrogen atoms, when present in a compound, are in *N*-oxide form, i.e., $N \rightarrow O$.

Also within the scope of this invention are a composition containing one or more of the compounds described above for use in treating an IL-12 overproduction-related disorder, and the use of such a composition for the manufacture of a medicament for the just-described use.

Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

The compounds described above can be prepared by methods well known in the art, as well as by the synthetic routes disclosed herein. For example, a purine compound (i.e., each of U and V is N, A is NR^e , and B is N. U, V, A, B and R^e are as defined in Summary) is prepared by using 2,4,8-trichloropurine as a starting material.

The three chloro groups can be displaced by various substituents. More specifically, the most reactive chloro group (i.e., chloro at position 4) is substituted with a morpholino group to form morpholinopurine. Further reaction of morpholinopurine with a primary or secondary aromatic amine affords a desired compound. In another example, a purine compound is synthesized by reacting 4,8-dichloropurine subsequently with morpholine, a primary or secondary amine, halogen (e.g., bromine), and another primary or secondary amine, or an aryloxy agent (e.g., sodium phenoxide). In further another example, a compound described in Summary is prepared by reacting 3,4-diaminopyrimidine with an arylisocyanate (e.g., *m*-tolyl isocyanate) or aryldithioiminocarbonate (e.g., dimethyl N-(*m*-tolyl)-dithioiminocarbonate).

The chemicals used in the above-described synthetic routes may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

A compound thus obtained can be further purified by flash column chromatography, high performance liquid chromatography, or crystallization.

Also within the scope of this invention is a pharmaceutical composition that contains an effective amount of one or more of the compounds described in Summary and a pharmaceutically acceptable carrier. Further, the present invention covers a method of administering an effective amount of such a compound to a subject in need

of treatment of IL-12 overproduction related diseases (e.g., rheumatoid arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or insulin-dependent diabetes mellitus). The term "treating" is defined as the application or administration of a composition including the aforementioned compound to a subject, who has a IL-12
5 related disease, a symptom of the disease, or a predisposition toward the disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptoms of the disease, or the predisposition toward the disease. "An effective amount" refers to the amount of the compound which is required to confer a therapeutic effect on the treated subject. The interrelationship of
10 dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich *et al.*, (1966) *Cancer Chemother Rep* 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardley, N.Y., 1970, 537. An effective amount of the compound described in Summary can range from about 0.001
15 mg/Kg to about 1000 mg/Kg. Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments such as use of other agents.

To practice the method of the present invention, a compound described above,
20 as a component of a pharmaceutical composition, can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

25 A sterile injectable composition, for example, a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for
30 example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions
5 can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

10 A composition for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule
15 form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according to techniques well-
20 known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. A compound delineated herein can also be administered in the form of suppositories for rectal administration.

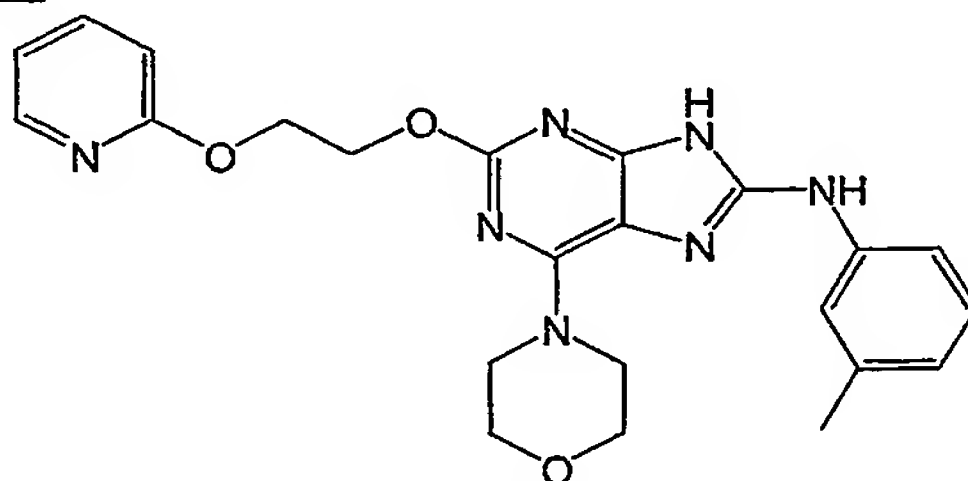
25 The carrier in the pharmaceutical composition must be "acceptable" in the sense of being compatible with the active ingredient of the formulation (and preferably, capable of stabilizing it) and not deleterious to the subject to be treated. For example, solubilizing agents such as cyclodextrins, which form specific, more soluble complexes with the compounds delineated herein, or one or more solubilizing
30 agents, can be utilized as pharmaceutical excipients for delivery of the compounds. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

The biological activities of a compound delineated herein can be evaluated by a number of cell-based assays. One of such assays can be conducted using cells from human peripheral blood mononuclear cells (PBMC) or human monocytic cell line (THP-1). The cells are stimulated with a combination of human interferon- γ (IFN γ) and lipopolysaccharide or a combination of IFN γ and *Staphylococcus aureus* Cowan I in the presence of a test compound. The level of inhibition of IL-12 production can be measured by determining the amount of p70 by using a sandwich ELISA assay with anti-human IL-12 antibodies. IC₅₀ of the test compound can then be determined. Specifically, PBMC or THP-1 cells are incubated with the test compound. Cell viability was assessed using the bio-reduction of MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium] (Promega, Madison, WI).

A compound described above can also be evaluated by animal studies. For example, one of such studies involves the ability of a test compound to treat adjuvant arthritis (i.e., a IL-12 overproduction related disorder) in rats.

Without further elaboration, it is believed that the above description has adequately enabled the present invention. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All of the publications cited herein are hereby incorporated by reference in their entirety.

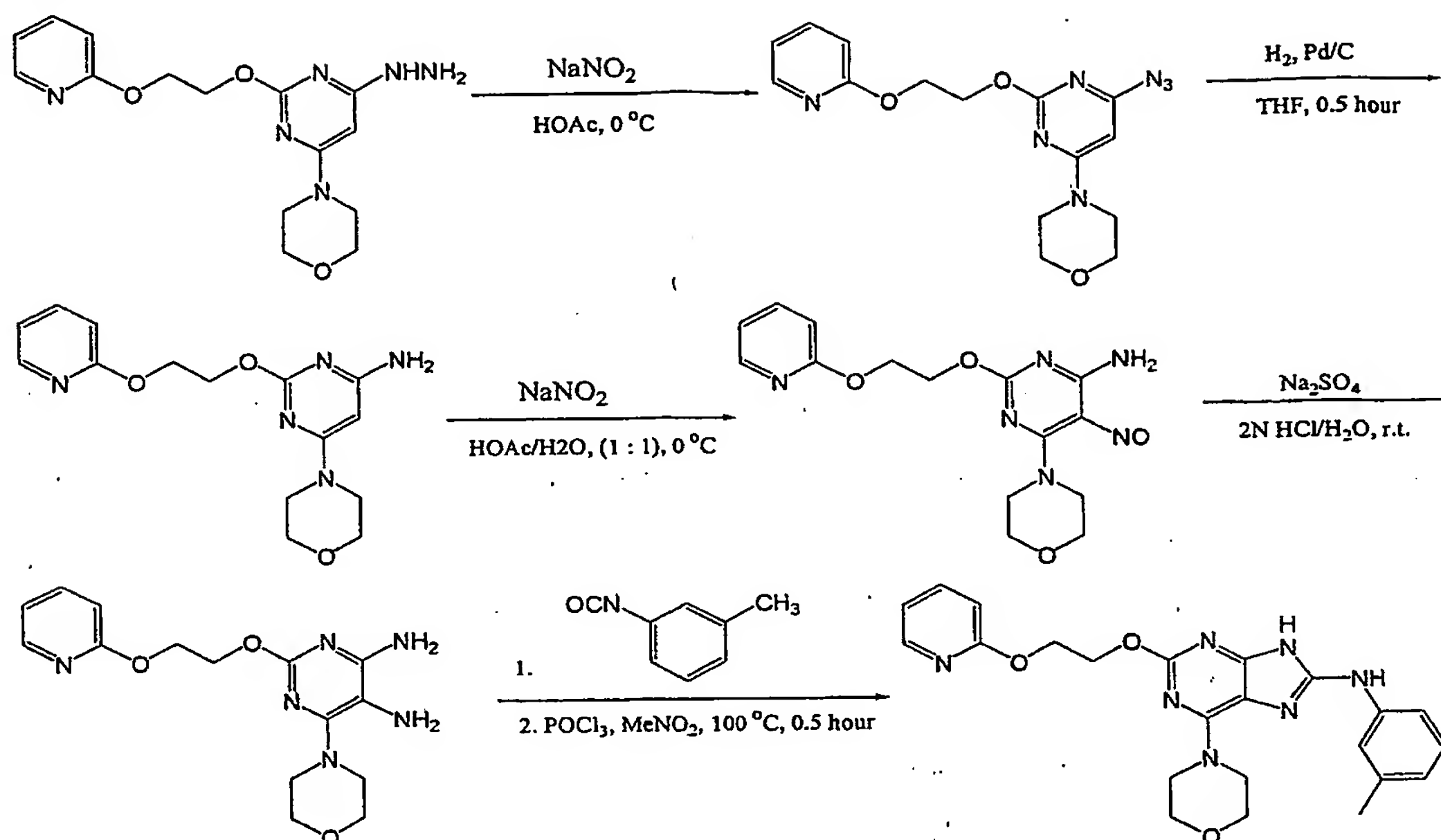
Example 1. Preparation of {6-morpholin-4-yl-2-[2-(pyridin-2-yloxy)-ethoxy]-9H-purin-8-yl}-m-tolyl-amine



The title compound was synthesized by one of the following two methods:

Method A:

Scheme 1



As shown in Scheme 1 above, to a solution of 2-[2-(pyridin-2-yloxy)-ethoxy]-6-hydrazino-4-morpholinopyrimidine (4.98 g, 15.00 mmol, 1.00 equiv.) in 40 mL HOAc was added NaNO₂ (1.553 g, 22.50 mmol, 1.50 equiv.) in six portions over a period of 1 hour. The reaction mixture was stirred at room temperature for 1 hour, and subjected to usual workup to yield 6-azido-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine as green viscous oil (5.0 g, 14.57 mmol, 97% yield). This oil was dissolved in 80 mL THF, and subjected to hydrogenation in the presence of 10% Pd on carbon (0.775 g of 10% Pd/C, 0.73 mmol, 0.05 equiv.) to yield 6-amino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine as light yellow solid (4.25 g, 13.4 mmol, 89% total yield).

¹H NMR (300 MHz, CDCl₃), δ (ppm): 8.11-8.14 (m, 1H); 7.57 (dd, *J* = 6.9 Hz, 2.1 Hz, 1H); 7.54 (dd, *J* = 5.4 Hz, 2.1 Hz, 1H); 8.00 (s, 1H); 6.87-6.75 (m, 2H); 5.23 (s, 1H); 4.93 (br s, 2H); 4.62 (s, 4H); 3.72-3.75 (m, 4H); 3.48-3.52 (m, 4H).

6-Amino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine (1.90 g, 6.00 mmol, 1.0 equiv.) was dissolved in 8 mL HOAc, and 8 mL H₂O was added. The solution was cooled to 0 °C, and NaNO₂ (0.414 g, 6.00 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at 0 °C for 1 hour. Water (20 mL) was added to dilute the slurry, and the solid was collected by filtration, washed with water, EtOAc

(2 mL), then dried to yield 6-amino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholino-5-nitroso-pyrimidine (1.47 g, 4.25 mmol, 85% yield) as blue solid. The nitroso compound (1.385 g, 4.00 mmol, 1.0 equiv.) was treated with 5 mL water and enough 2 N HCl so that a clear dark blue solution was formed. Na₂S₂O₄ (2.79 g, 16.00 mmol, 4.0 equiv.) was added in three portions, and the solution was stirred at room temperature for 1 hour. The resulting clear yellow solution was carefully neutralized with cold 2 M NaOH solution, and subjected to EtOAc extraction. 5, 6-Diamino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine (0.80 g, 2.41 mmol, 60%) was obtained as light yellow solid after usual workup.

¹H NMR (300 MHz, CDCl₃), δ (ppm): 8.12-8.14 (m, 1H); 7.52-7.58 (m, 1H); 6.83-6.87 (m, 1H); 6.75-6.78 (m, 1H); 4.57-4.65 (m, 6H); 3.79-3.83 (m, 4H); 3.22-3.26 (m, 4H); 2.71 (br s, 2H).

ESMS calcd. for C₁₅H₂₁N₆O₃ 332.1; Found: 333.1 (M+H)⁺.

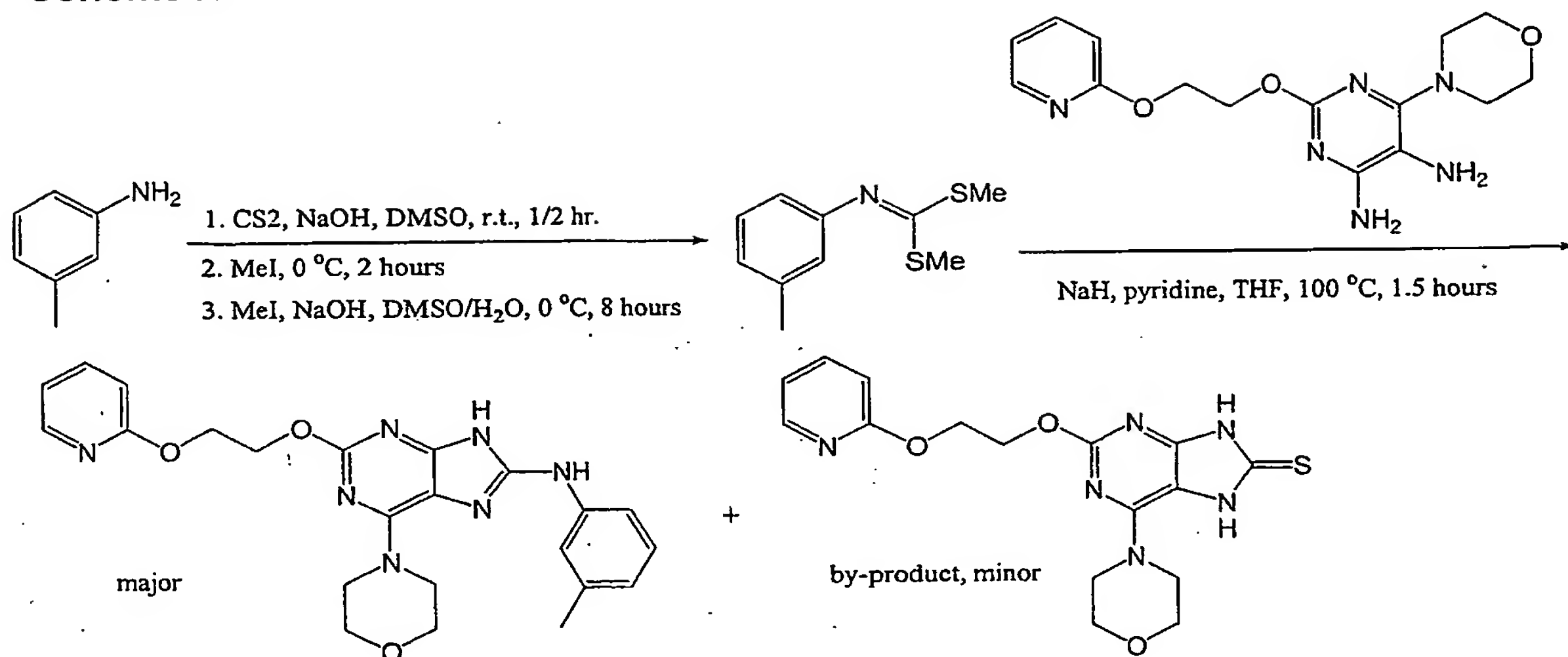
5, 6-Diamino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine (0.332 g, 1.00 mmol, 1.00 equiv.) and *m*-tolyl isocyanate (0.133 g, 1.00 mmol, 1.00 equiv.) were mixed in 10 mL THF and stirred at room temperature for 15 hours. THF was removed, and the residue was treated with POCl₃ in 2 mL CH₃NO₂ at 100°C for 30 minutes. The reaction mixture was neutralized with 2N NaOH solution at 0°C, and subjected to EtOAc extraction. The organic solution was dried over MgSO₄, filtered through a plug of silica gel, concentrated to around 2 mL, and cooled to 0°C, resulting in formation of the titled compound as off-white crystal which was collected by filtration, washed with EtOAc, and dried (0.095 g, 0.212 mmol, 21.2% yield).

¹H NMR (300 MHz, DMSO-d₆), δ (ppm): 11.70 (s, 1H); 9.10 (s, 1H); 8.16-8.18 (m, 1H); 7.69-7.75 (m, 1H); 7.43 (s, 1H); 7.35 (d, *J* = 8.1 Hz, 1H); 7.14 (t, *J* = 7.8 Hz, 1H); 6.97-7.01 (m, 1H); 6.85 (d, *J* = 7.8 Hz, 1H); 6.71 (d, *J* = 7.8 Hz, 1H); 4.52-4.57 (m, 4H); 4.09 (br s, 4H); 3.69-3.72 (m, 4H); 2.27 (s, 3H).

ESMS calcd. for C₂₃H₂₆N₇O₃: 447.2; Found: 448.2 (M+H)⁺.

Method B:

Scheme 2

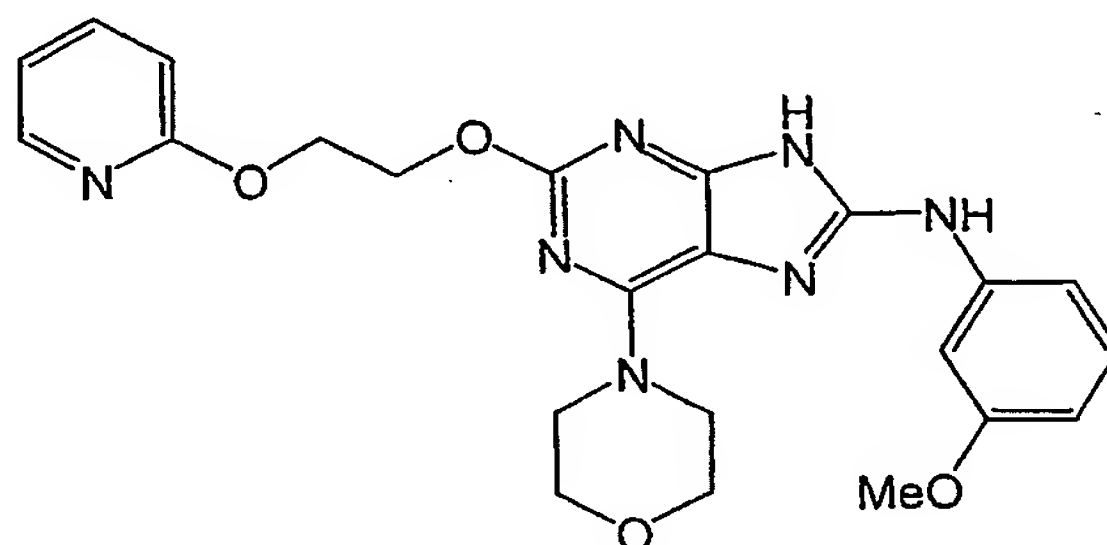


5 As shown in Scheme 2 above, 5, 6-diamino-2-[2-(pyridin-2-yloxy)-ethoxy]-4-morpholinopyrimidine (0.166 g, 0.5 mmol, 1.00 equiv.), dimethyl N-(*m*-tolyl)-dithioiminocarbonate (0.106 g, 0.5 mmol, 1.00 equiv., prepared from *m*-toluidine, CS₂, NaOH and MeI), pyridine (0.2 mL), and THF (5 mL) were mixed in a sealed tube. NaH (0.12 g 60% in oil, 3 mmol, 6.0 equiv) was added in the presence of

10 nitrogen gas. The mixture was sealed in the tube, and heated at 100°C for 1.5 hours. The titled compound was isolated as white solid (0.090 g, 0.20 mmol, 40% yield) after workup and purification. A side product, 6-morpholin-4-yl-2-[2-(pyridin-2-yloxy)-ethoxy]-7,9-dihydro-purine-8-thione, was also isolated as a white solid (0.018g, 0.048mmol, 10% yield).

15

Example 2. Preparation of (3-methoxyphenyl)-{6-Morpholin-4-yl-2-[2-(pyridin-2-yloxy)-ethoxy]-9H-purin-8-yl}-amine

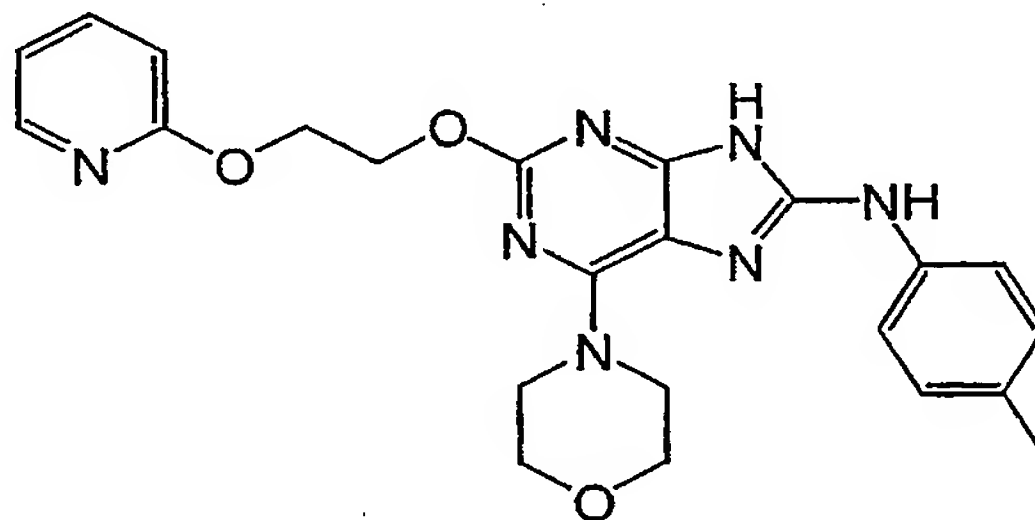


The title compound was synthesized as light brown solid in the same manner as described in Example 1, Method A.

¹H NMR (300 MHz, DMSO-d₆), δ (ppm): 11.73 (s, 1H), 9.28 (s, 1H), 8.16-8.18 (m, 1H), 7.69-7.75 (m, 1H), 7.58 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 6.97-7.01 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.44-6.47 (m, 1H), 4.50-4.60 (m, 4H), 4.10 (br s, 4H), 3.73 (s, 3H), 3.66-3.72 (m, 4H).

ESMS calcd for C₂₃H₂₄N₇O₄: 463.2; Found: 462.2(M-H)⁻.

Example 3. Preparation of {6-Morpholin-4-yl-2-[2-(pyridin-2-yloxy)-ethoxy]-9H-purin-8-yl}-*p*-tolyl-amine

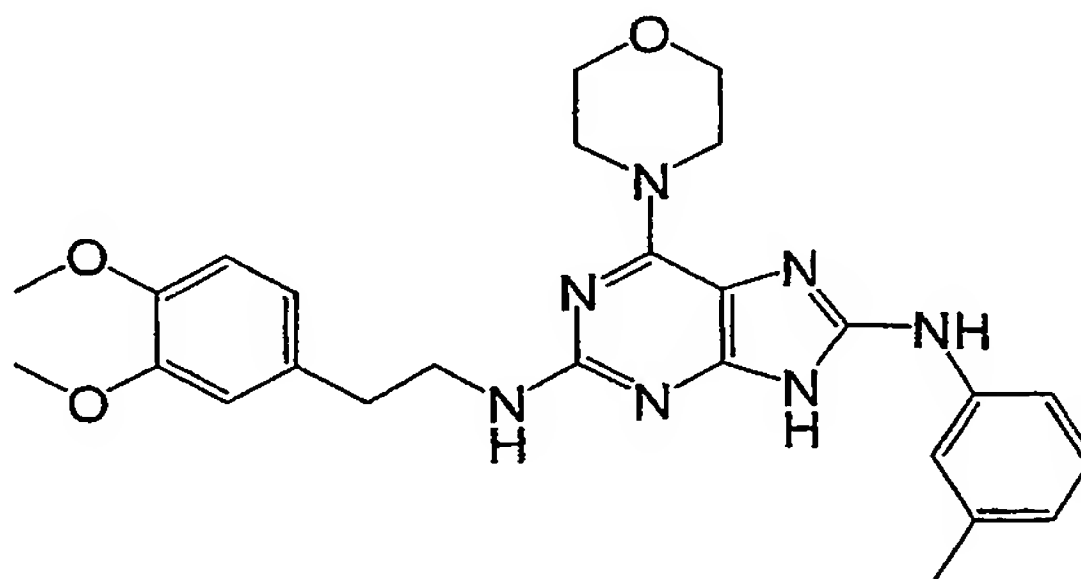


The title compound was synthesized as light brown solid in the same manner as described in Example 1, Method A.

¹H NMR (300 MHz, acetone-d₆), δ (ppm): 10.6 (s, 1H), 8.45 (br s, 1H), 8.11-8.20 (m, 1H), 7.58-7.70 (m, 3H), 7.05-7.15 (m, 2H), 6.92-6.97 (m, 1H), 6.75-6.80 (m, 1H), 4.57-4.67 (m, 4H), 4.18 (br s, 4H), 3.72-3.78 (m, 4H), 2.26 (s, 3H).

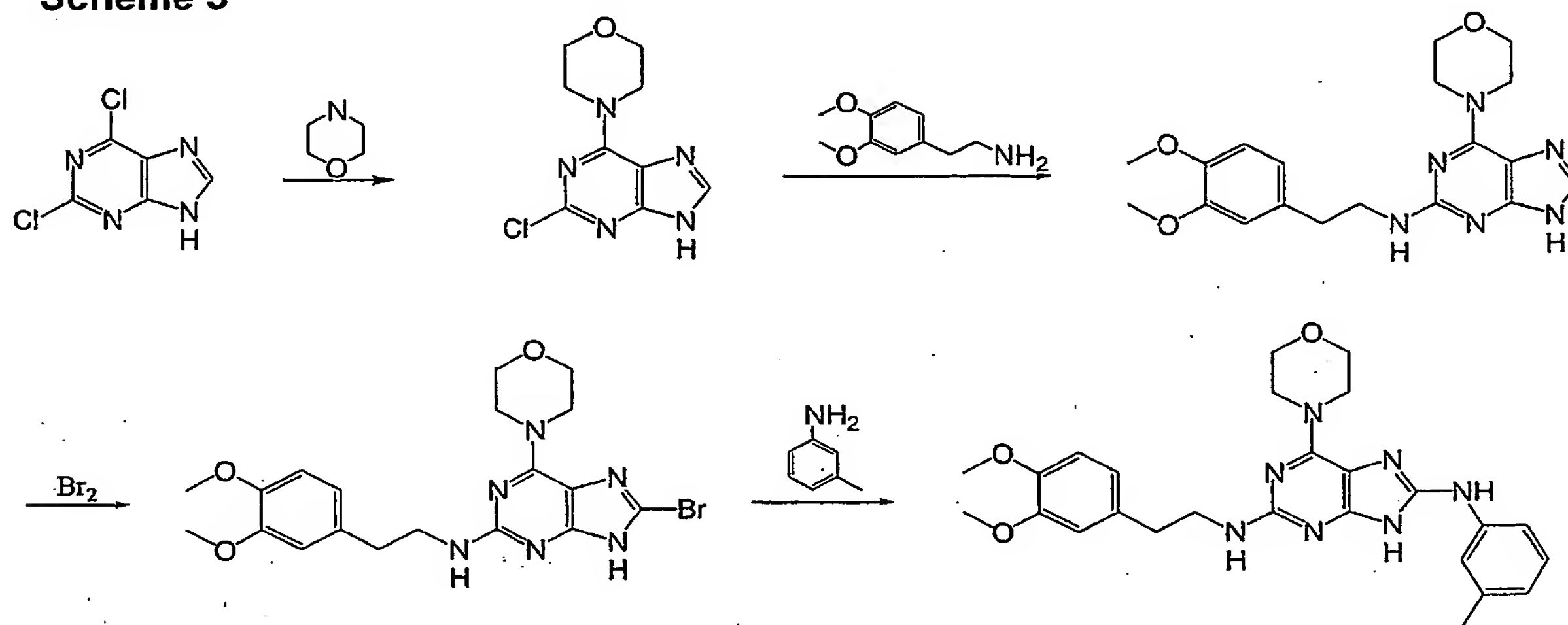
ESMS calcd for C₂₃H₂₆N₇O₃: 448.2; Found: 448.2 (M+H)⁺.

Example 4. Preparation of N²-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-morpholin-4-yl-N⁸-*p*-tolyl-9H-purine-2,8-diamine



The title compound was synthesized by the method shown in Scheme 3

Scheme 3



As shown in Scheme 3 above, a mixture of 2,6-dichloropurine (1.90 g, 10 mmol) and morpholine (2.34 g, 30 mmol) in water (25 mL) was heated under reflux for 15 min. Solidified reaction mixture was cooled to room temperature. Solid was filtered out and washed with water, methanol and ether. The 2-chloro-6-morpholin-4-yl-9H-purine was obtained in 96% yield (2.30 g). A mixture of 2-chloro-6-morpholin-4-yl-9H-purine (1.92 g, 8 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (4.35 g, 24 mmol) in sealed tube and under nitrogen was stirred at 190-195°C for 1 hour. The reaction mixture turned to clear solution initially and then formed a slurry. The reaction mixture was cooled to room temperature diluted with methanol (8 mL) and the solid was collected by filtration, washed with methanol and Et₂O and dried to afford 2.30 g (74% yield) of [2-(3,4-dimethoxy-phenyl)-ethyl]-(6-morpholin-4-yl-9H-purin-2-yl) amine.

¹H NMR (DMSO-d₆) δ (ppm), 12.22 (bs, 1H), 7.69 (d, *J*=9.0Hz, 1H), 6.86-6.73 (m, 3H), 6.30-6.22 (m, 1H), 4.12 (bs, 4H), 3.74-3.69 (m, 10H), 3.43 (t, *J*=6.0Hz, 2H), 2.78-2.73 (m, 2H).

ESMS calcd for C₁₉H₂₄N₆O₃: 384.19; Found: 385.2 (M+H)⁺.

To a solution of [2-(3,4-dimethoxy-phenyl)-ethyl]-(6-morpholin-4-yl-9H-purin-2-yl) amine (1.16 g, 3 mmol) in dioxane (75 mL) was added bromine (0.180 mL, 3.3 mmol) in dioxane (5 mL) dropwise over a period of 1 hour. The mixture was stirred at room temperature for additional 4 hours and diluted with water (25 mL) and

extracted with EtOAc. The organic phase was washed with brine, water, dried over Na₂SO₄. The solvent was evaporated in *vacuo* and solid was washed with methanol to give (8-bromo-6-morpholin-4-yl-9H-purin-2-yl)-[2-(3,4-dimethoxy-phenyl)-ethyl]-amine as a white solid (1.05 g, 75% yield).

5 ¹H NMR (DMSO-d₆) δ (ppm), 6.86-6.72 (m, 3H), 6.50-6.42 (m, 1H), 4.05 (bs, 4H), 3.75-3.69 (m, 10H), 3.44-3.38 (m, 2H), 2.78-2.74 (m, 2H).

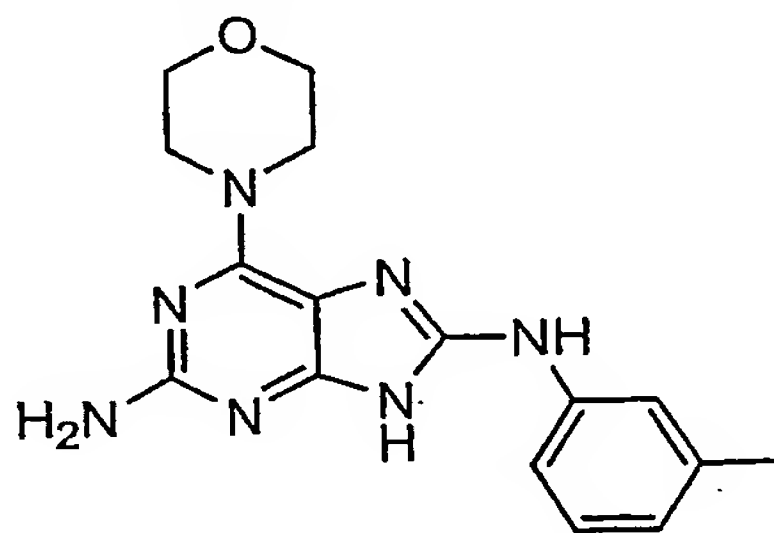
ESMS calcd for C₁₉H₂₃BrN₆O₃: 462.10; Found: 463.0 (M+H)⁺.

A mixture of (8-bromo-6-morpholin-4-yl-9H-purin-2-yl)-[2-(3,4-dimethoxy-phenyl)-ethyl]-amine (0.93 g, 2 mmol) and *m*-toluidine (0.86 mL, 8 mmol) in sealed
10 tube and under nitrogen was stirred at 190-195°C for 1 hour. The reaction mixture was cooled to room temperature diluted with methanol (5 mL) and the solid was collected by filtration, washed with small amount of methanol and Et₂O and dried to give 0.76 g of N²-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-morpholin-4-yl-N⁸-p-tolyl-9H-purine-2,8-diamine in 78% yield.

15 ¹H NMR (DMSO-d₆) δ (ppm), 11.62 (bs, 1H), 9.46 (s, 1H), 7.38-7.18 (m, 4H), 6.86-6.70 (m, 4H), 3.82-3.34 (m, 16H), 2.77 (t, *J*=6.0Hz, 2H), 2.27 (s, 3H).

ESMS calcd for C₂₆H₃₁N₇O₃: 489.25; Found: 490.2 (M+H)⁺.

Example 5. Preparation of 6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-diamine.

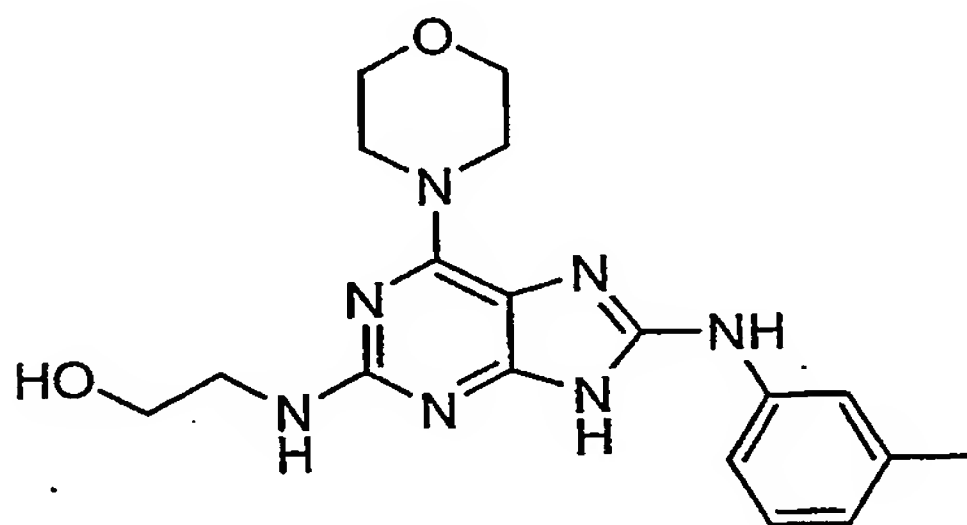


The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 9.15 (bs, 1H), 7.40-7.32 (m, 2H), 7.19-7.16 (m, 1H), 6.76-6.74 (m, 1H), 3.97 (bs, 4H), 3.74-3.72 (m, 4H), 2.27(s, 3H).

ESMS calcd for C₁₆H₁₉N₇O: 325.17; Found: 326.1 (M+H)⁺.

Example 6. Preparation of 2-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-ylamino)-ethanol

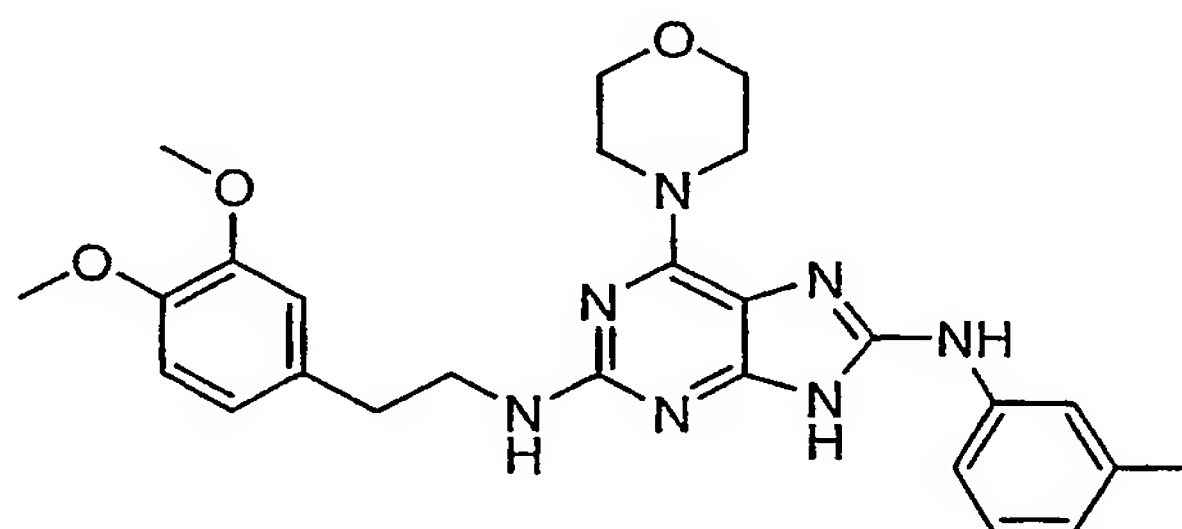


The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 11.64 (bs, 1H), 9.49 (s, 1H), 7.39-7.34 (m, 2H), 7.21 (t, J=7.2 Hz, 1H), 6.86-6.80 (m, 1H), 3.90-3.72 (m, 8H), 3.55 (t, J=6.0Hz, 2H), 3.42-3.38 (m, 2H), 2.29 (s, 3H).

ESMS calcd for C₁₈H₂₃N₇O₂: 369.19; Found: 370.1 (M+H)⁺.

Example 7. Preparation of N²-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-diamine



5

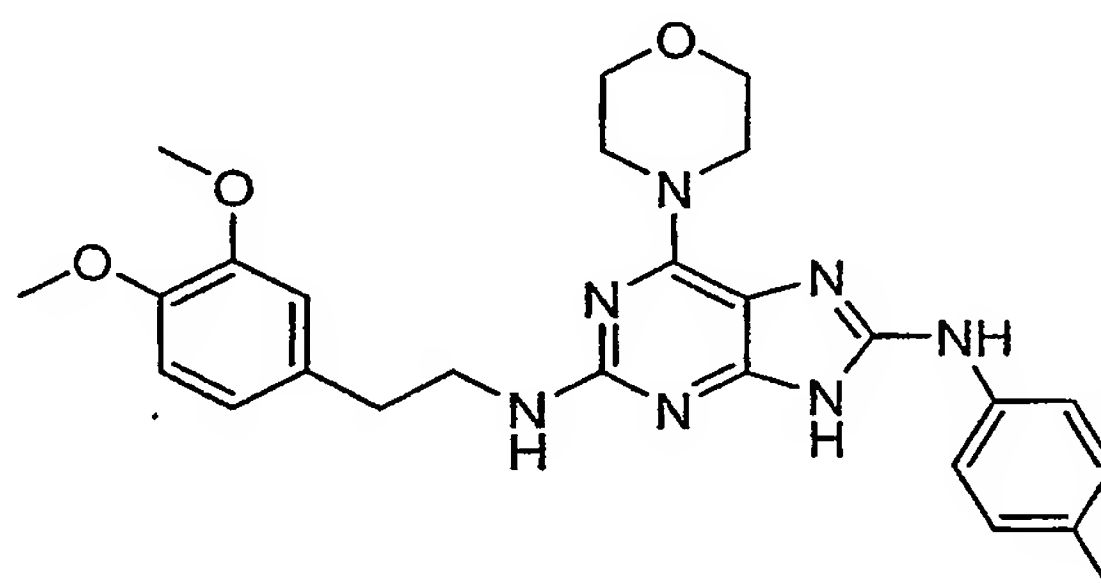
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 11.65 (bs, 1H), 9.50 (s, 1H), 7.42-7.20 (m, 4H), 6.84-6.65 (m, 4H), 3.82-3.40 (m, 16H), 2.82-2.78 (m, 2H), 2.28(s, 3H).

ESMS calcd for C₂₆H₃₁N₇O₃: 489.25; Found: 490.2 (M+H)⁺.

10

Example 8. Preparation of N²-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-morpholin-4-yl-N⁸-p-tolyl-9H-purine-2,8-diamine



15

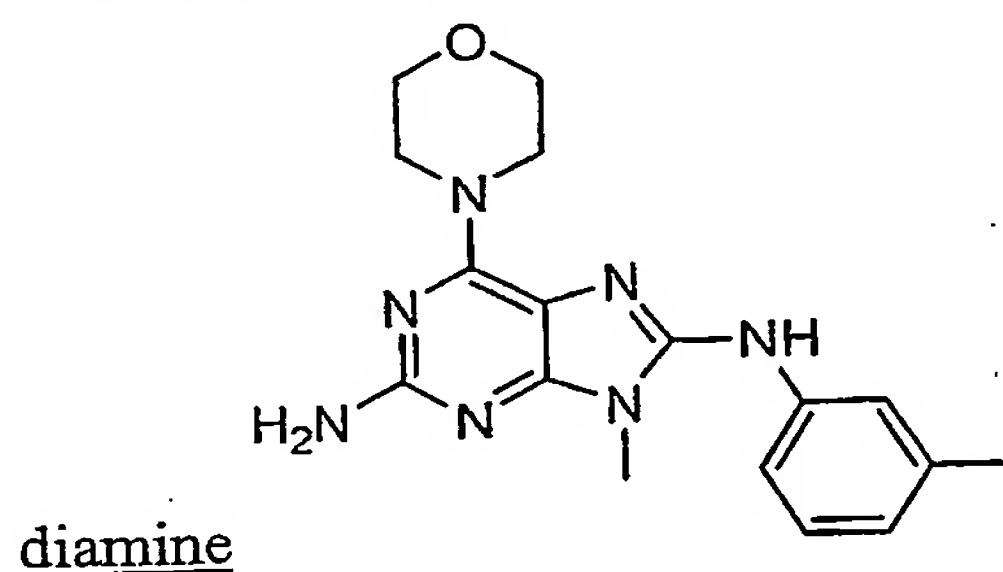
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 11.62 (bs, 1H), 9.46 (s, 1H), 7.38-7.18 (m, 4H), 6.86-6.70 (m, 4H), 3.82-3.34 (m, 16H), 2.77 (t, J=6.0Hz, 2H), 2.27(s, 3H).

ESMS calcd for C₂₆H₃₁N₇O₃: 489.25; Found: 490.2 (M+H)⁺.

20

Example 9. Preparation of 9-methyl-6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-

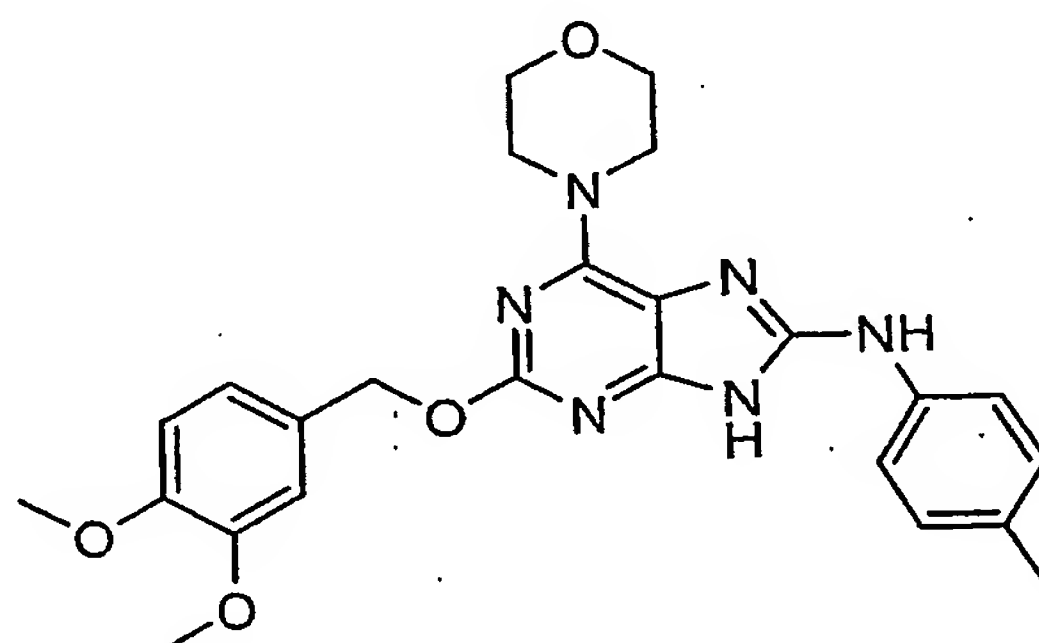


The title compound was prepared by a method as delineated herein.

¹H-NMR (DMSO-d₆) δ (ppm), 9.25 (bs, 1H), 7.40-7.32 (m, 2H), 7.22-7.16 (m, 2H), 6.76-6.72 (m, 1H), 3.97 (m, 7H), 3.74-3.72 (m, 4H), 2.27 (s, 3H).

ESMS calcd for C₁₇H₂₁N₇O: 339.18; Found: 340.2 (M+H)⁺.

Example 10. Preparation of [2-(3,4-dimethoxy-benzyloxy)-6-morpholin-4-yl-9H-purin-8-yl]-p-tolyl-amine

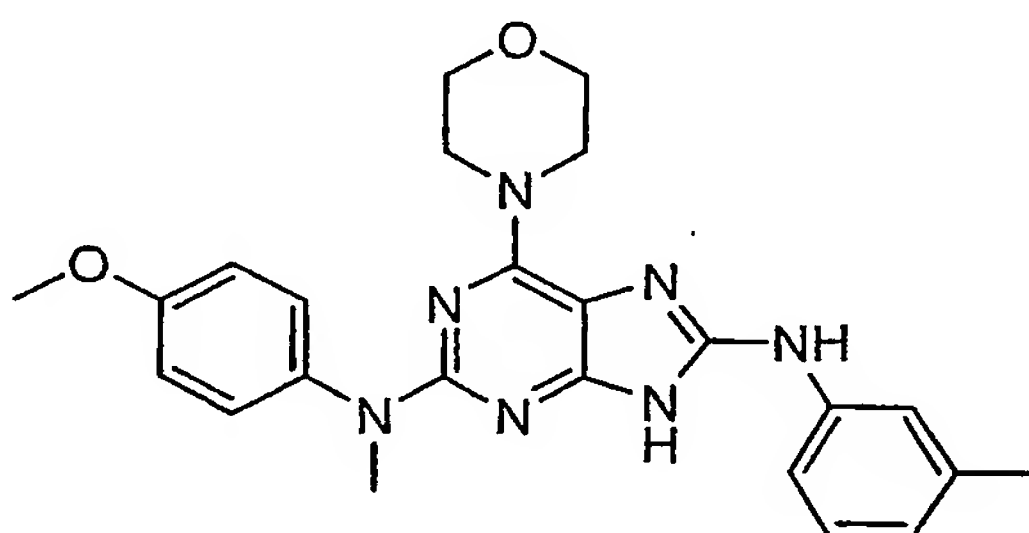


The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 11.63 (s, 1H), 9.03 (s, 1H), 7.48-7.45 (m, 2H), 7.08-6.94 (m, 5H), 5.10 (s, 2H), 3.74-3.69 (m, 14H), 2.23 (s, 3H).

ESMS calcd for C₂₅H₂₈N₆O₄: 476.22; Found: 477.2 (M+H)⁺.

Example 11. Preparation of N²-(4-methoxy-phenyl)-N²-methyl-6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-diamine



5

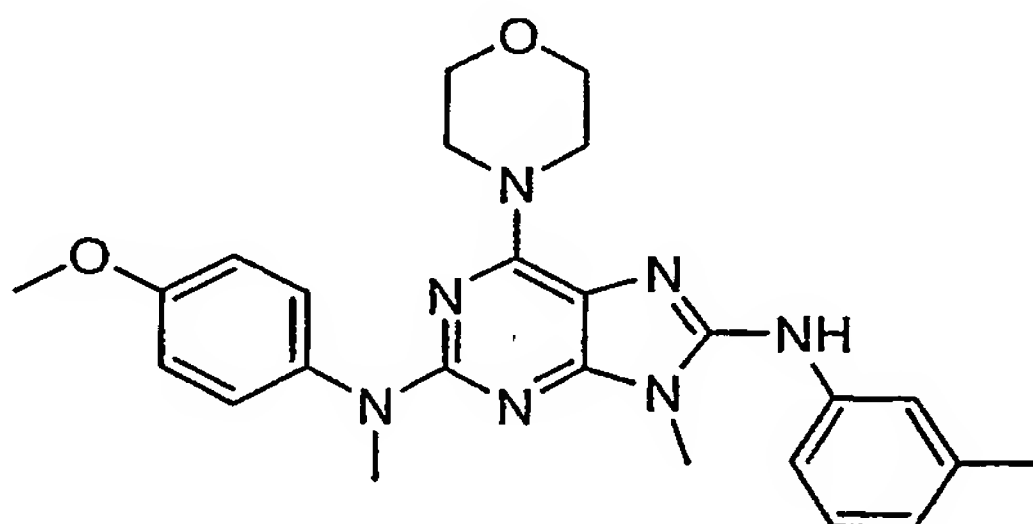
The title compound was prepared by a method as delineated herein.

¹H NMR (CDCl₃) δ (ppm), 9.37 (bs, 1H), 7.33-7.25 (m, 2H), 7.16-7.09 (m, 3H), 7.02-6.98 (m, 2H), 6.84-6.82 (m, 1H), 4.06-3.82 (m, 10H), 3.48-3.40 (m, 4H), 2.25 (s, 3H).

10

ESMS calcd for C₂₄H₂₇N₇O₂: 445.22; Found: 446.2 (M+H)⁺.

Example 12. Preparation of N²-(4-methoxy-phenyl)-N²-methyl-9-methyl-6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-diamine



15

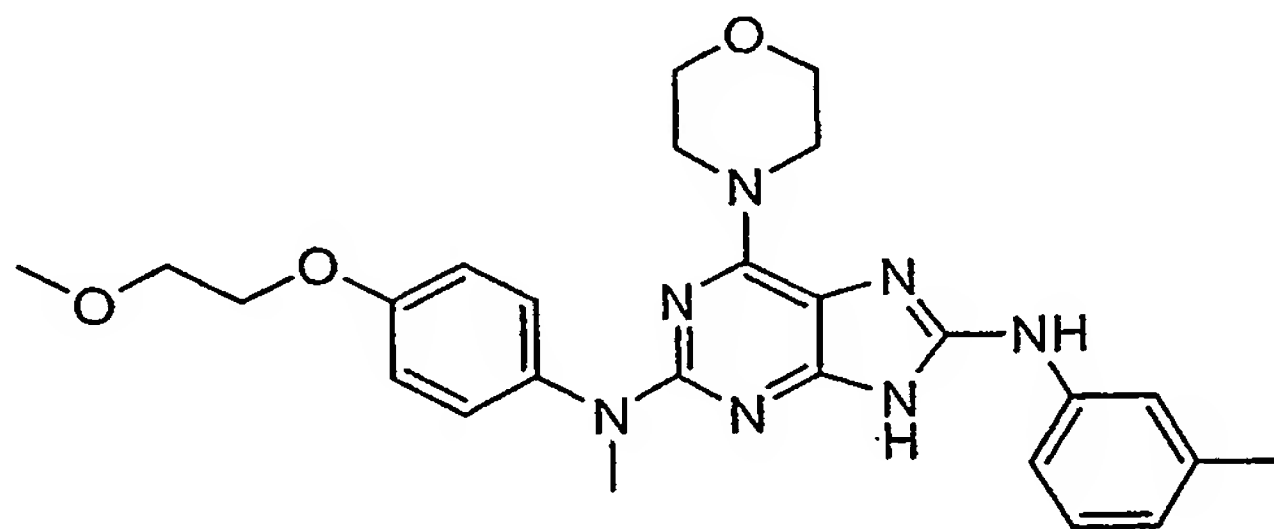
The title compound was prepared by a method as delineated herein.

¹H NMR (CDCl₃) δ (ppm), 7.38-7.07 (m, 5H), 6.95-6.8 (m, 3H), 5.94 (s, 1H), 4.20-4.05 (m, 4H), 3.81 (s, 3H), 3.78-3.75 (m, 4H), 3.51 (s, 3H), 3.44 (s, 3H), 2.30 (s, 3H).

20

ESMS calcd for C₂₅H₂₉N₇O₂: 459.24; Found: 460.2 (M+H)⁺.

Example 13. Preparation of N²-[4-(2-Methoxy-ethoxy)-phenyl]-N²-methyl-6-morpholin-4-yl-N⁸-m-tolyl-9H-purine-2,8-diamine



5

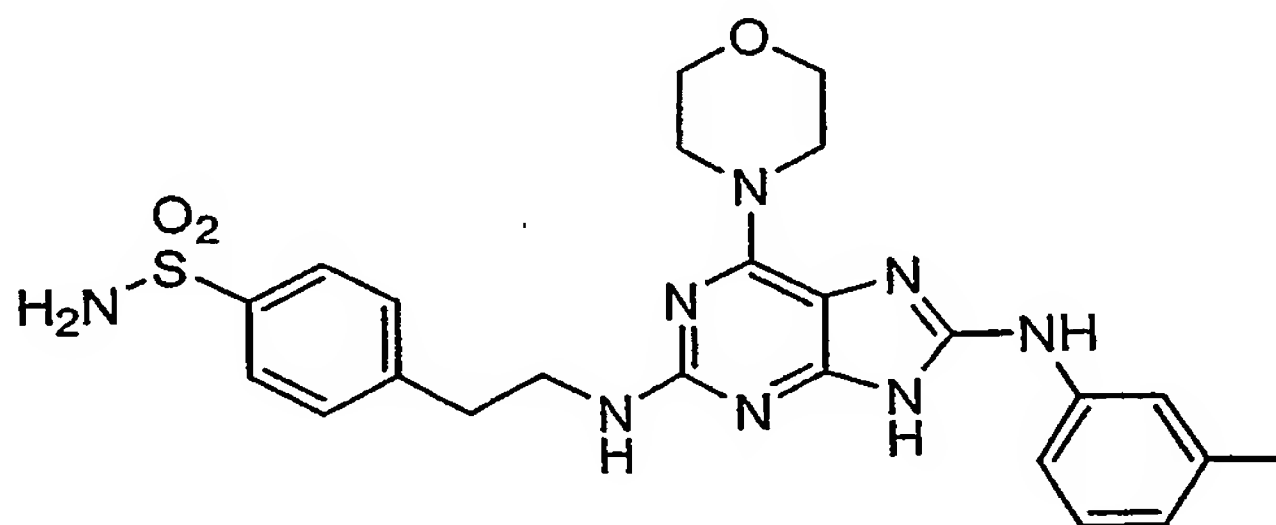
The title compound was prepared by a method as delineated herein.

¹H NMR (CDCl₃) δ (ppm), 9.20 (bs, 1H), 7.33-7.25 (m, 2H), 7.18-7.14 (m, 2H), 7.06-7.03 (m, 2H), 6.86-6.82 (m, 2H), 4.20-4.05 (m, 4H), 3.90-3.72 (m, 8H), 3.52 (s, 3H), 3.45 (s, 3H), 2.25 (s, 3H).

10

ESMS calcd for C₂₆H₃₁N₇O₃: 489.25; Found: 490.2 (M+H)⁺.

Example 14. Preparation of 4-[2-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-ylamino)-ethyl]-benzenesulfonamide



15

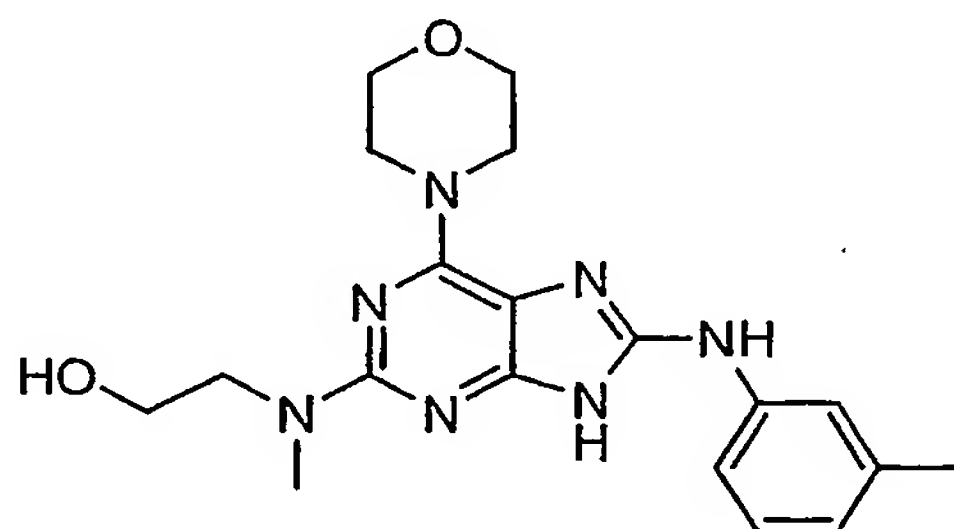
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 11.64 (bs, 1H), 9.50 (s, 1H), 7.73 (d, J=8.1 Hz, 2H), 7.42-7.17 (m, 8H), 6.82 (bs, 1H), 3.82-3.36 (m, 10H), 2.92 (t, J=7.2 Hz, 2H), 2.27 (s, 3H).

20

ESMS calcd for C₂₄H₂₈N₈O₃S: 508.20; Found: 509.2 (M+H)⁺.

Example 15. Preparation of 2-[methyl-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-yl)-amino]-ethanol



5

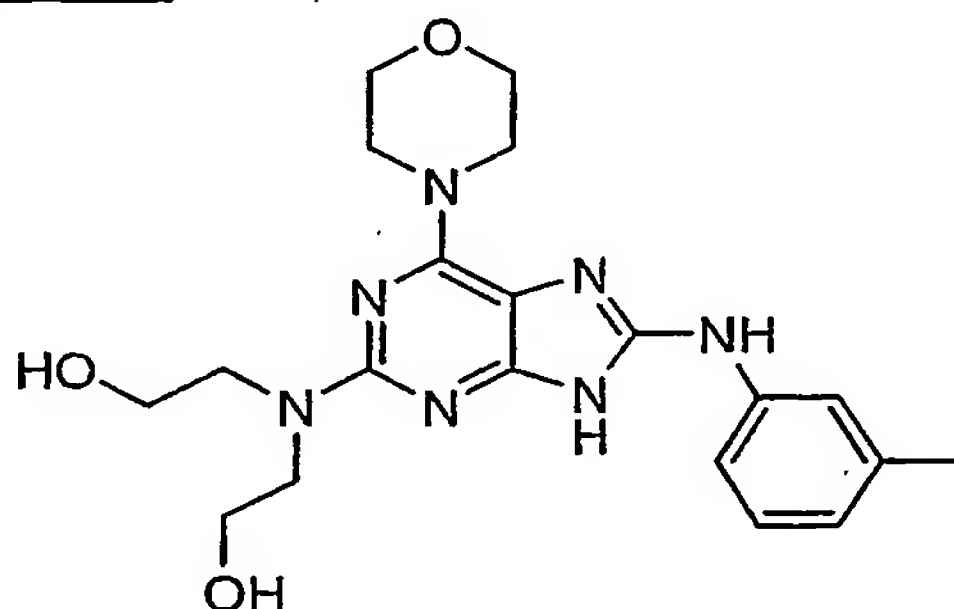
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 9.60 (s, 1H), 7.43-7.22 (m, 3H), 6.86-6.82 (m, 1H), 6.60-6.50 (m, 1H), 4.33 (t, $J=7.2\text{Hz}$, 2H), 3.94-3.72 (m, 10H), 2.99 (s, 3H), 2.29 (s, 3H).

10

ESMS calcd for $\text{C}_{19}\text{H}_{25}\text{N}_7\text{O}_2$: 383.21; Found: 384.2 ($\text{M}+\text{H}$) $^+$.

Example 16. Preparation of 2-[(2-hydroxy-ethyl)-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-yl)-amino]-ethanol



15

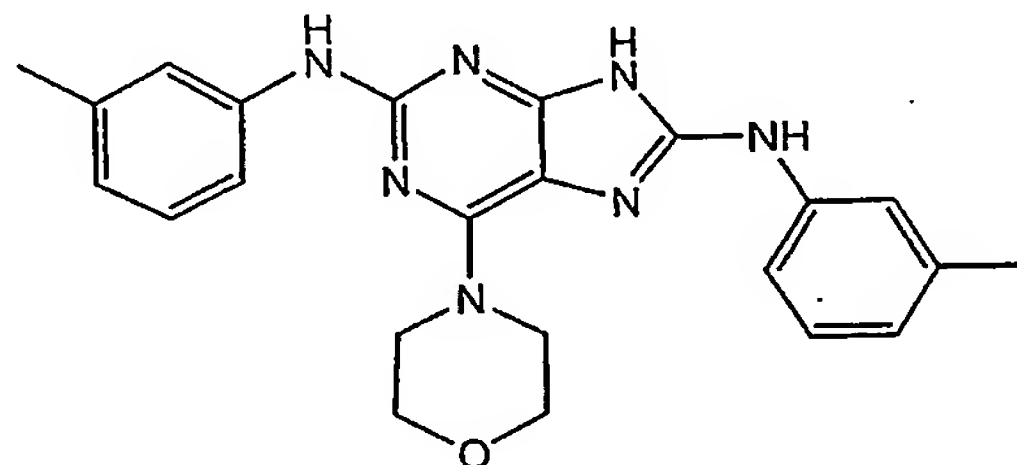
The title compound was prepared by a method as delineated herein.

^1H NMR (CDCl_3) δ (ppm), 10.62 (bs, 1H), 9.46(s, 1H), 7.38-7.07 (m, 4H), 4.24-4.15 (m, 4H), 3.94-3.90 (m, 4H), 3.82-3.77 (m, 8H), 2.27 (s, 3H).

ESMS calcd for $\text{C}_{20}\text{H}_{27}\text{N}_7\text{O}_3$: 413.22; Found: 414.4 ($\text{M}+\text{H}$) $^+$.

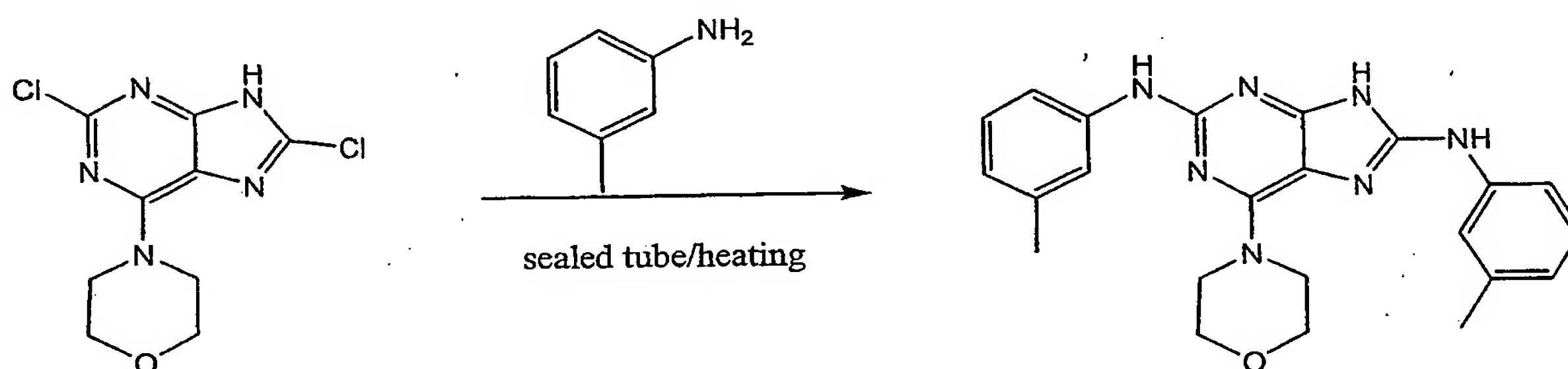
20

Example 17. Preparation of 6-morpholin-4-yl- N^2, N^8 -di-*m*-tolyl-9*H*-purine-2, 8-diamine



The title compound was prepared by the method shown in Scheme 4.

Scheme 4

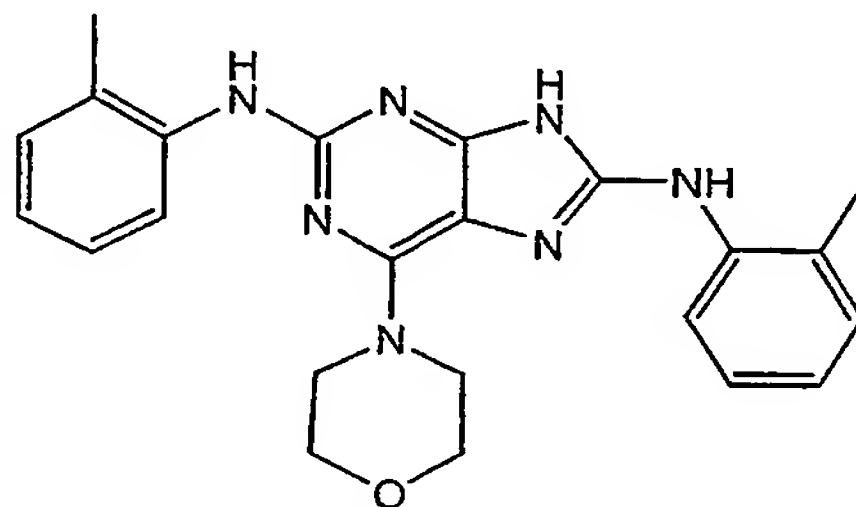


As shown in Scheme 4, a mixture of 2,8-dichloro-6-morpholin-4-yl-9*H*-purine (412 mg, 1.5 mmol) and *m*-tolylamine (0.97 mL, 9.0 mmol, 6 equiv.) was placed into a sealed tube filled with N_2 . The sealed tube was submerged into an oil bath (180°C). After 1.5 hours, the mixture in the sealed tube solidified. The sealed tube was cooled down to room temperature followed by adding ethyl acetate (10 mL) into the mixture. The resulting suspension was stirred for 1 hour at room temperature. The solid was collected by filtration and washed with cold methanol/water (5:1) and ethyl acetate. A total of 480 mg pale yellow powder was obtained. Yield was 78%.

1H NMR (CD_3OD) δ (ppm), 7.20-7.42 (m, 6H), 6.85-7.00 (m, 2H), 3.96-3.99 (m, 4H), 3.80-3.85 (m, 4H), 2.34-2.35 (m, 6H).

ESMS calcd for $C_{23}H_{25}N_7O$: 415.21; Found: 416.2 ($M+H$) $^+$.

Example 18. Preparation of 6-morpholin-4-yl-*N*², *N*⁸-di-*o*-tolyl-9*H*-purine-2, 8-diamine

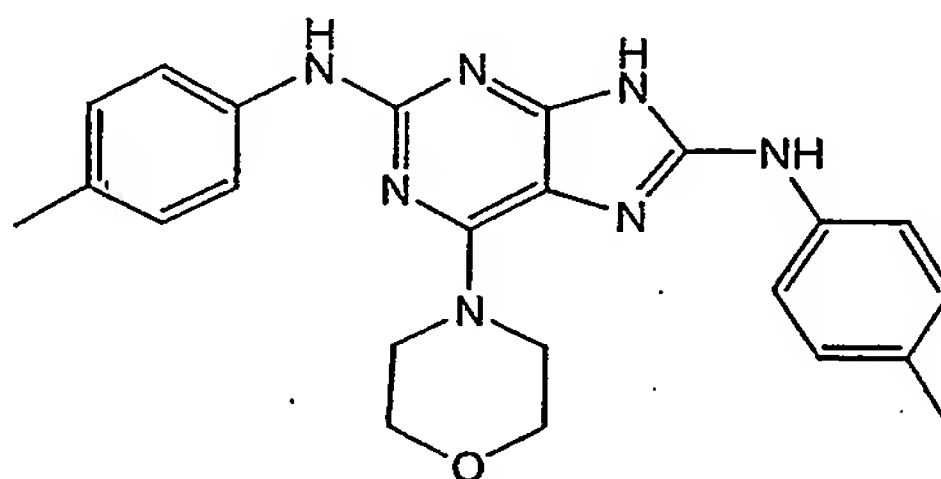


5 The title compound was prepared by a method as delineated herein.

¹H-NMR (CDCl₃) δ (ppm), 7.98 (br., 1H), 7.58 (br., 1H), 6.98-7.11 (m, 8H), 6.44 (br., 1H), 4.00-4.11 (m, 4H), 3.70-3.80 (m, 4H), 2.15-2.39 (m, 6H)/

ESMS calcd for C₂₃H₂₅N₇O: 415.21; Found: 416.2 (M+H)⁺.

10 Example 19. Preparation of 6-morpholin-4-yl-*N*², *N*⁸-di-*p*-tolyl-9*H*-purine-2, 8-diamine

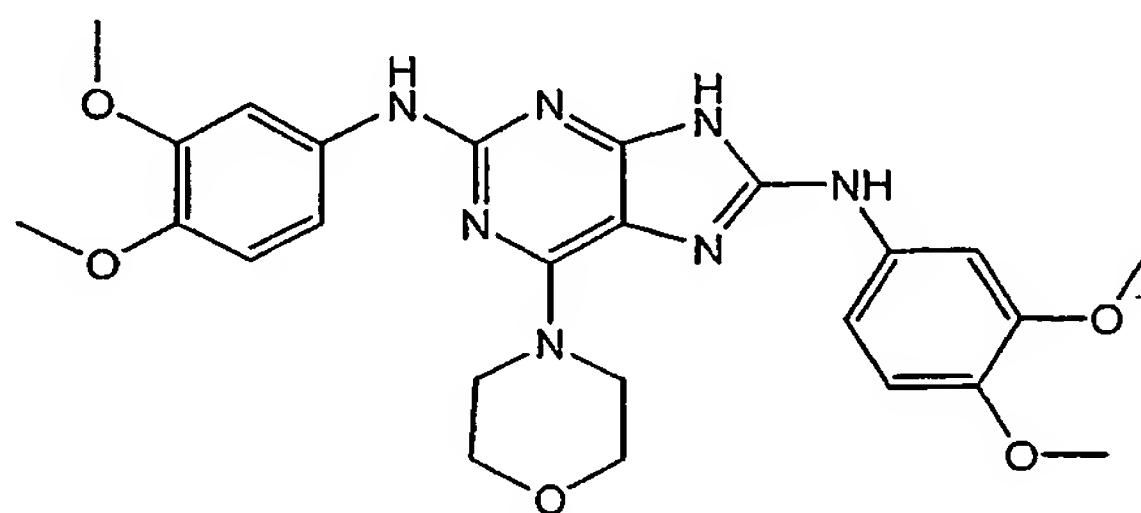


The title compound was prepared by a method as delineated herein.

15 ¹H-NMR (CD₃OD) δ (ppm), 7.34-7.45 (dd, *J*=8.4, 25.8 Hz, 4H), 7.15-7.21 (dd, *J*=8.4, 9.0 Hz, 4H), 3.92 (m, 4H), 3.80-3.83 (m, 4H), 2.32-2.34 (m, 6H).

ESMS calcd for C₂₃H₂₅N₇O: 415.21; Found: 416.2 (M+H)⁺.

Example 20. Preparation of N^2, N^8 -bis-(3,4-dimethoxy-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



5

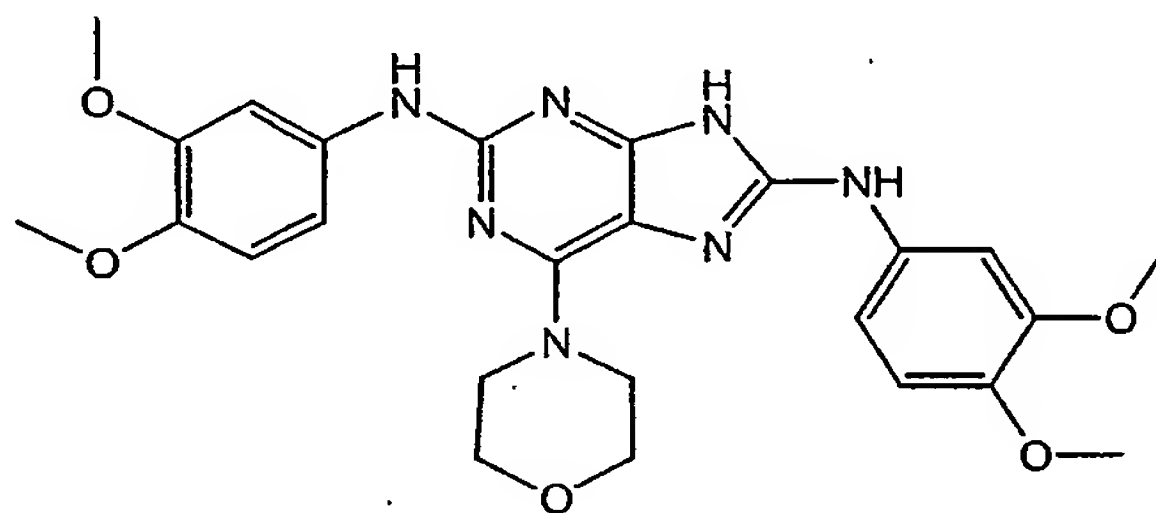
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 7.43 (br., 1H), 7.27 (br., 1H), 6.34-7.09 (m, 7H), 3.75-4.00 (m, 20H).

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}_5$: 507.22; Found: 508.2 ($\text{M}+\text{H}$) $^+$.

10

Example 21. Preparation of N^2, N^8 -bis-(3,4-dimethoxy-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



15

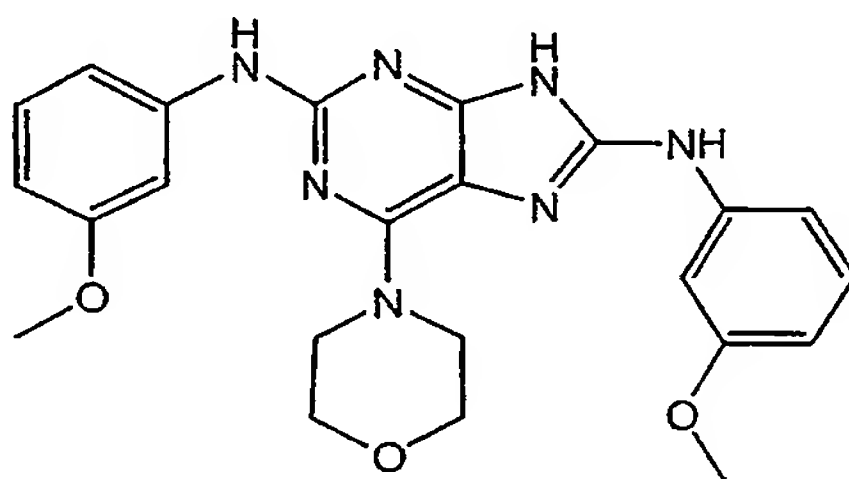
The title compound was prepared by a method as delineated herein.

^1H NMR (acetone- d_6) δ (ppm), 10.55 (br., 1H), 8.46 (d, $J=8.1\text{Hz}$, 2H), 7.92 (br., 1H), 7.29 (br., 1H), 6.85 (m, 2H), 6.65 (m, 2H), 4.25 (m, 4H), 3.75-3.89 (m, 10H), 2.28 (m, 6H)/

20

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}_3$: 475.23; Found: 476.2 ($\text{M}+\text{H}$) $^+$.

Example 22. Preparation of N^2, N^8 -bis-(3-methoxy-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



5

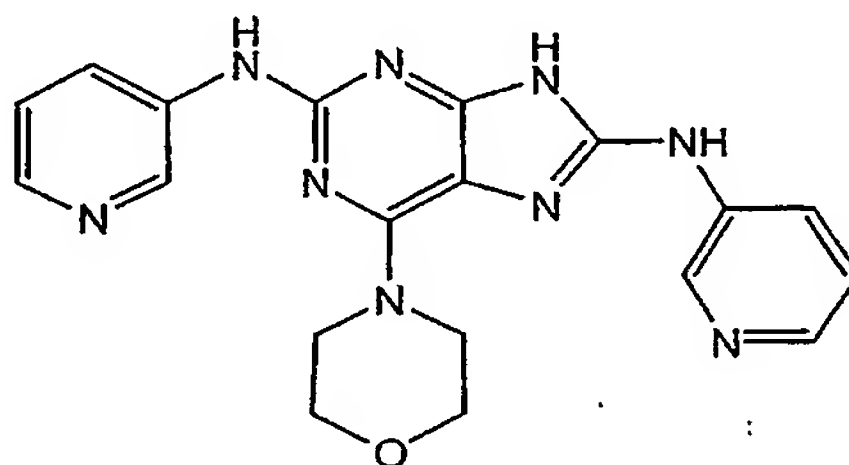
The title compound was prepared by a method as delineated herein.

^1H NMR (CD_3OD) δ (ppm), 7.19-7.35 (m, 4H), 7.02 -7.05 (m, 2H), 6.64-6.74 (m, 2H), 4.00 (m, 4H), 3.80-3.85 (m, 10H).

ESMS calcd for $\text{C}_{23}\text{H}_{25}\text{N}_7\text{O}_3$: 447.20; Found: 448.2 ($\text{M}+\text{H}$) $^+$.

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Example 23. Preparation of 6-morpholin-4-yl- N^2, N^8 -di-pyridin-3-yl-9H-purine-2,8-diamine



15

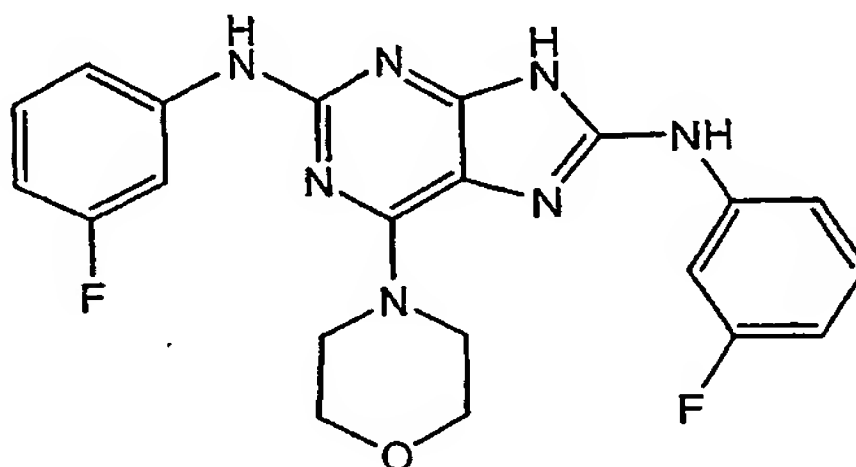
The title compound was prepared by a method as delineated herein.

^1H -NMR (CD_3OD) δ (ppm), 9.42 (s, 1H), 9.27 (d, $J=5.4\text{Hz}$, 1H), 9.15 (s, 1H), 9.00 (d, $J=5.4\text{Hz}$, 1H), 7.73-7.80 (m, 4H), 4.42 (m, 4H), 3.86-3.90 (m, 10H).

ESMS calcd for $\text{C}_{19}\text{H}_{19}\text{N}_9\text{O}$: 389.17; Found: 390.1 ($\text{M}+\text{H}$) $^+$.

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Example 24. Preparation of N^2, N^8 -bis-(3-fluoro-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



5

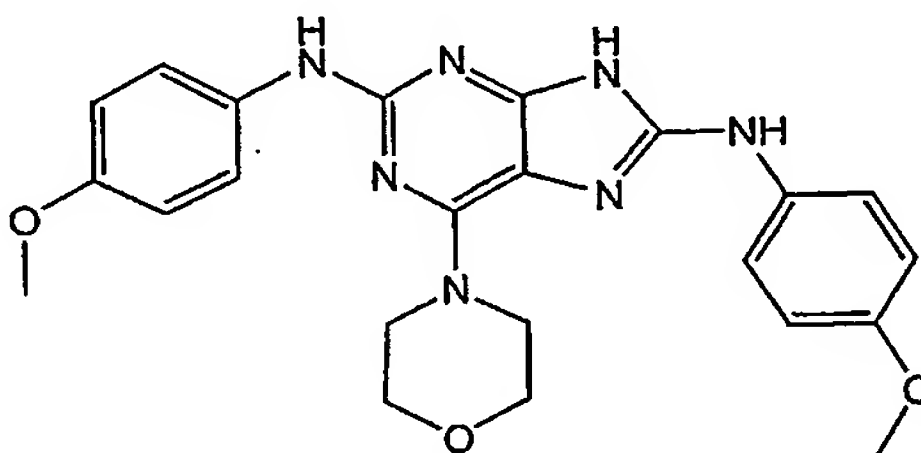
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 9.58 (br., 1H), 9.28 (br., 1H), 7.78 (d, $J=9.3\text{Hz}$, 1H), 7.59 (d, $J=9.3\text{Hz}$, 1H), 7.25-7.42 (m, 4H), 6.68-6.71 (m, 2H), 4.09 (m, 4H), 3.75-3.77 (m, 4H)/

10

ESMS calcd for $\text{C}_{21}\text{H}_{19}\text{F}_2\text{N}_7\text{O}$: 423.16; Found: 424.1 ($\text{M}+\text{H}$) $^+$.

Example 25. Preparation of N^2, N^8 -bis-(4-methoxy-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



15

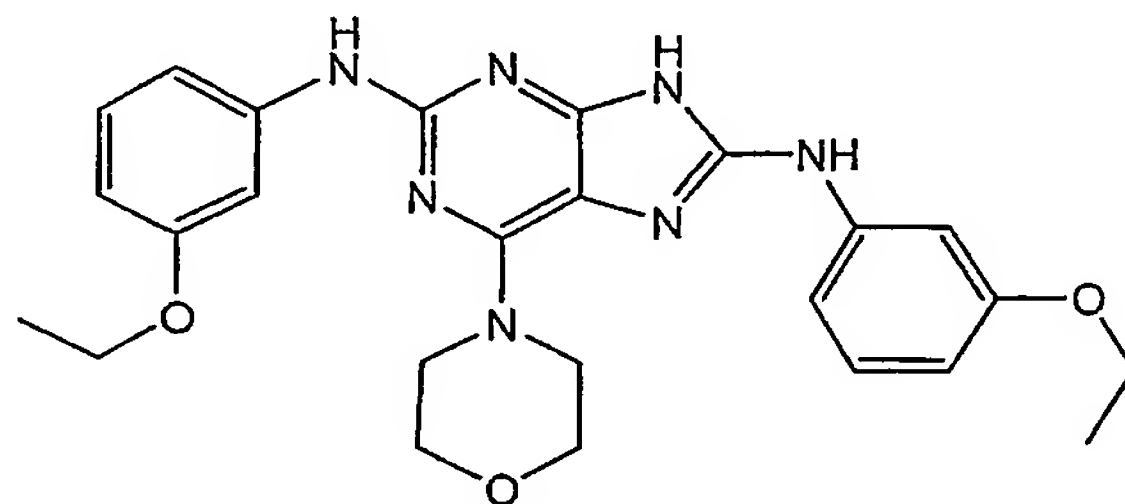
The title compound was prepared by a method as delineated herein.

^1H -NMR (DMSO- d_6) δ (ppm), 9.40 (br., 2H), 7.52 (m, 4H), 6.90 (m, 4H), 3.60-3.90 (m, 14H).

20

ESMS calcd for $\text{C}_{23}\text{H}_{25}\text{N}_7\text{O}_3$: 447.20; Found: 448.2 ($\text{M}+\text{H}$) $^+$.

Example 26. Preparation of N^2, N^8 -bis-(3-ethoxy-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



5

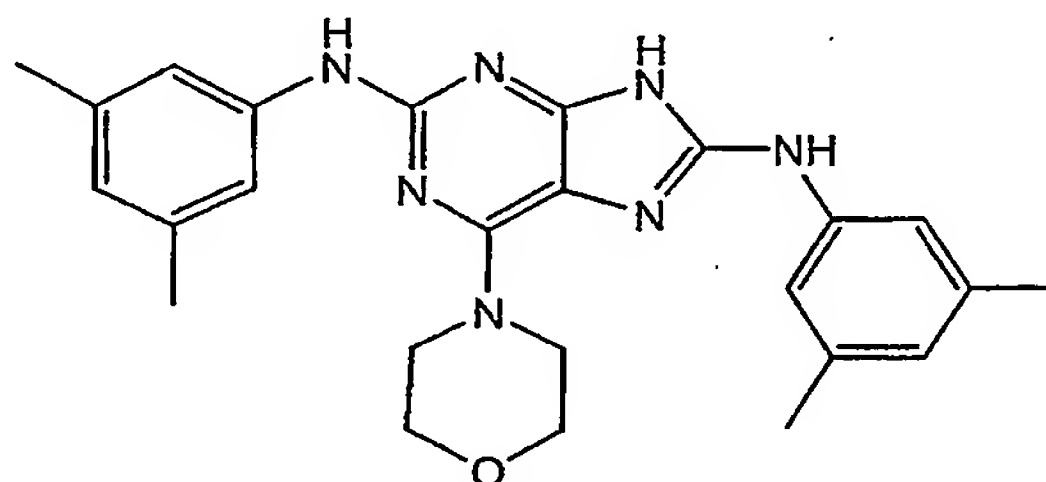
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 9.40 (br., 2H), 7.48-7.54 (m, 2H), 6.90-7.20 (m, 4H), 6.55 (m, 2H), 3.75-4.10 (m, 12H), 1.33 (t, $J=6.9\text{Hz}$, 6H).

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}_3$: 475.23; Found: 476.2 ($\text{M}+\text{H}$) $^+$.

10

Example 27. Preparation of N^2, N^8 -bis-(3,5-dimethyl-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



15

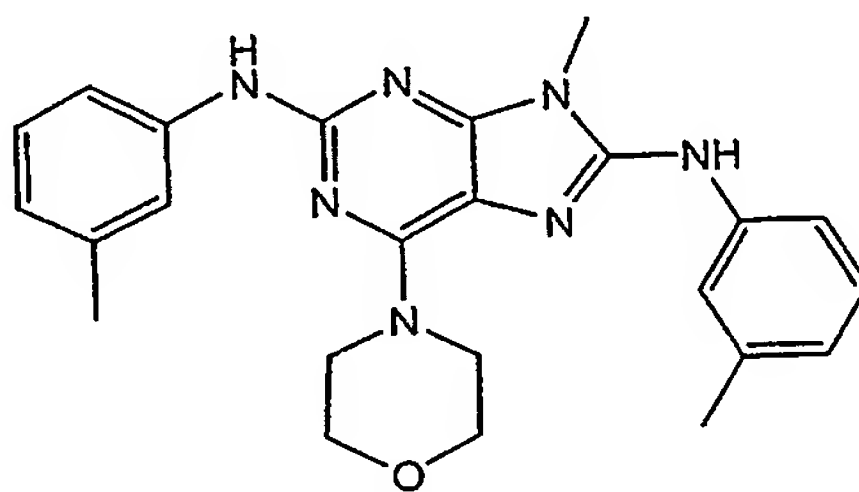
The title compound was prepared by a method as delineated herein.

^1H -NMR ($\text{CD}_3\text{OD}/\text{DMSO}-d_6$) δ (ppm), 7.37 (s, 4H), 7.22 (s, 4H), 6.55 (m, 2H), 6.49 (m, 2H), 4.15 (m, 4H), 3.74-3.77 (m, 4H), 2.22 (m, 12H).

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}$: 443.24; Found: 444.2 ($\text{M}+\text{H}$) $^+$.

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Example 28. Preparation of 9-methyl-6-morpholin-4-yl- N^2 , N^8 -di-*m*-tolyl-9*H*-purine-2,8-diamine



5

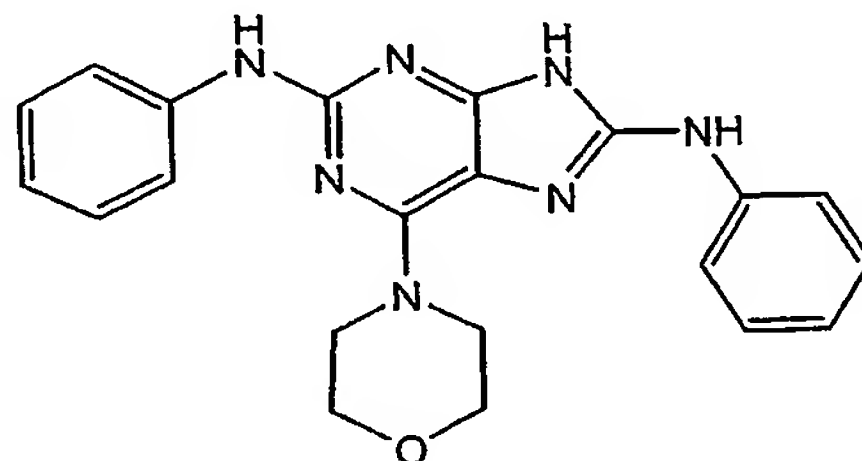
The title compound was prepared by a method as delineated herein.

$^1\text{H-NMR}$ (CD_3OD) δ (ppm), 7.45 (m, 2H), 7.11-7.22 (m, 4H), 6.77-6.82 (m, 2H), 4.19 (m, 4H), 3.82 (m, 4H), 3.52 (s, 3H), 2.30 (m, 6H).

ESMS calcd for $\text{C}_{24}\text{H}_{27}\text{N}_7\text{O}$: 429.23; Found: 430.2 ($\text{M}+\text{H}$) $^+$.

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Example 29. Preparation of 6-Morpholin-4-yl- N^2 , N^8 -diphenyl-9*H*-purine-2,8-diamine



15

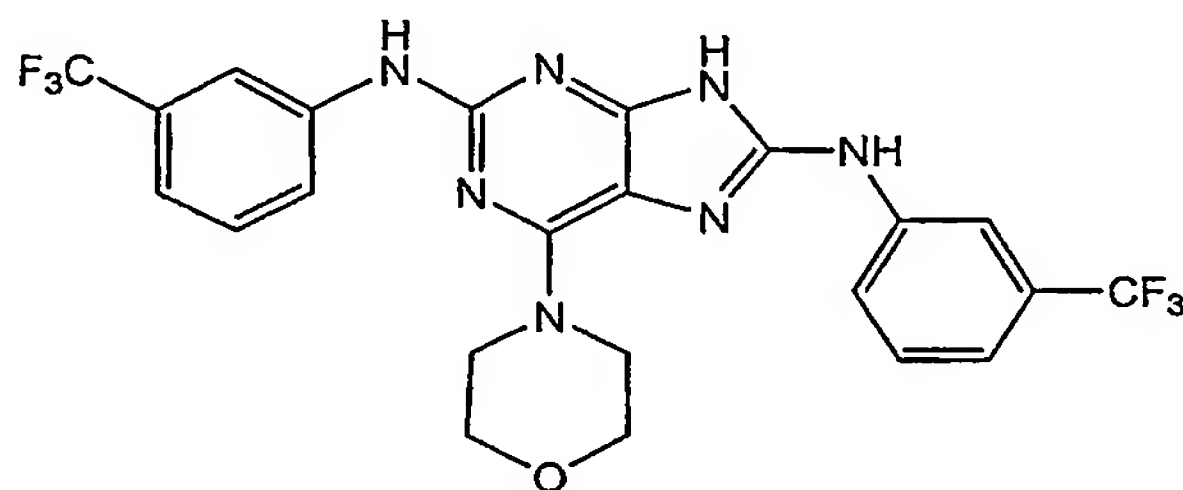
The title compound was prepared by a method as delineated herein.

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm), 9.62 (br., 2H), 7.59 (m, 4H), 7.33 (m, 4H), 7.05 (m, 2H), 3.99 (m, 4H), 3.76 (m, 4H).

ESMS calcd for $\text{C}_{21}\text{H}_{21}\text{N}_7\text{O}$: 387.18; Found: 388.2 ($\text{M}+\text{H}$) $^+$.

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Example 30. Preparation of 6-morpholin-4-yl- N^2, N^8 -bis-(3-trifluoromethyl-phenyl)-9H-purine-2,8-diamine



5

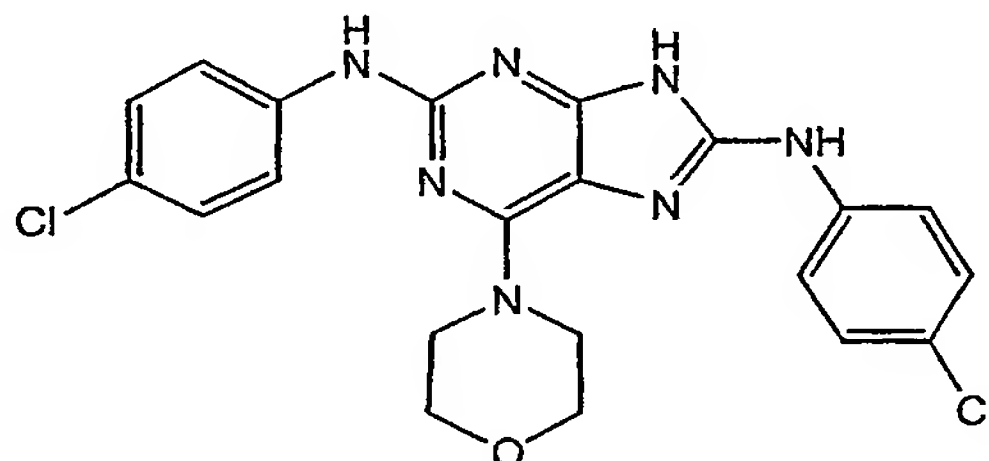
The title compound was prepared by a method as delineated herein.

^1H -NMR (DMSO- d_6) δ (ppm), 9.75 (br., 1H), 9.42 (br., 1H), 8.31 (m, 2H), 7.80 (m, 2H), 7.49 (m, 2H), 7.21 (m, 2H), 4.11 (m, 4H), 3.75 (m, 4H).

ESMS calcd for $\text{C}_{23}\text{H}_{19}\text{F}_6\text{N}_7\text{O}$: 523.16; Found: 524.2 ($\text{M}+\text{H}$) $^+$.

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Example 31. Preparation of N^2, N^8 -bis-(4-chloro-phenyl)-6-morpholin-4-yl-9H-purine-2,8-diamine



15

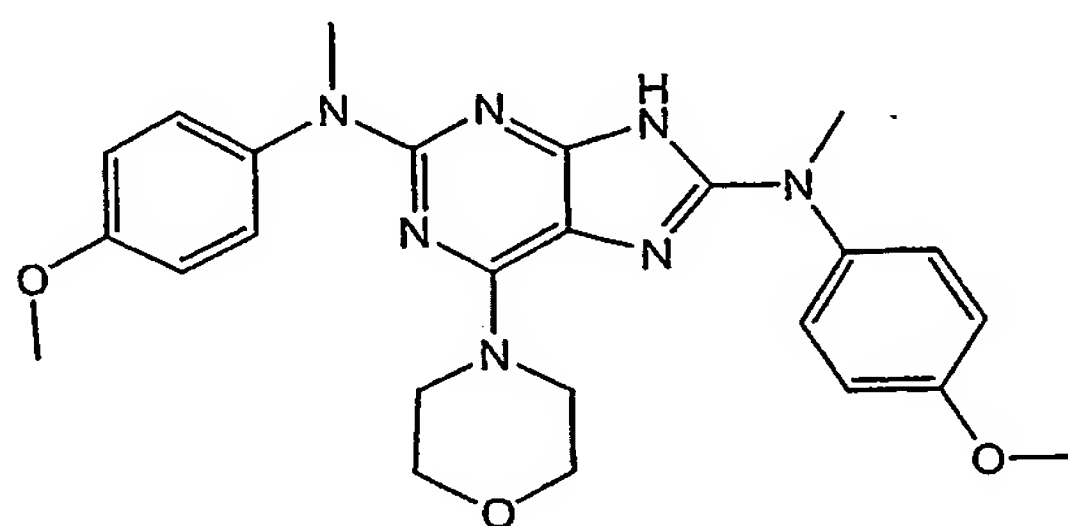
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 9.75 (br., 2H), 7.64 (m, 4H), 7.36 (m, 4H), 4.02 (m, 4H), 3.75 (m, 4H).

ESMS calcd for $\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_7\text{O}$: 455.10; Found: 456.0 ($\text{M}+\text{H}$) $^+$.

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Example 32. Preparation of N^2, N^8 -bis-(4-methoxy-phenyl)- N^2, N^8 -dimethyl-6-morpholin-4-yl-9H-purine-2,8-diamine



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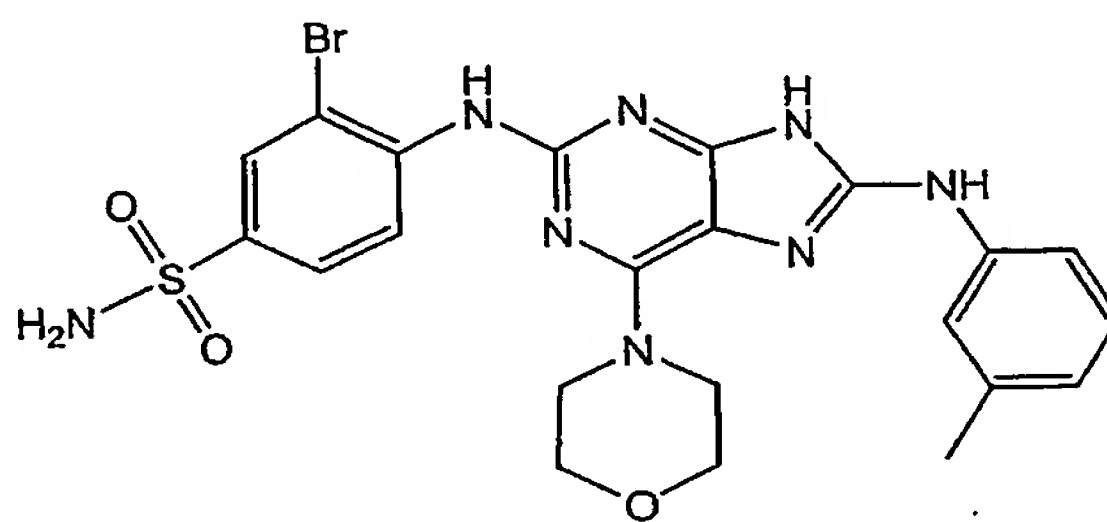
The title compound was prepared by a method as delineated herein.

^1H NMR (acetone- d_6) δ (ppm), 10.15 (br., 1H), 7.27 (AB, $J=8.7\text{Hz}$, 2H), 7.21 (AB, $J=8.7\text{Hz}$, 2H), 6.94 ((AB, $J=8.7\text{Hz}$, 2H), 6.86 (AB, $J=8.7\text{Hz}$, 2H), 4.04 (m, 4H), 3.79 (m, 6H), 3.68 (m, 4H), 3.38 (m, 6H).

10

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}_3$: 475.23; Found: 476.5 ($\text{M}+\text{H}$) $^+$.

Example 33. Preparation of 3-bromo-4-(6-morpholin-4-yl-8-*m*-tolylamino-9H-purin-2-ylamino)-benzenesulfonamide



15

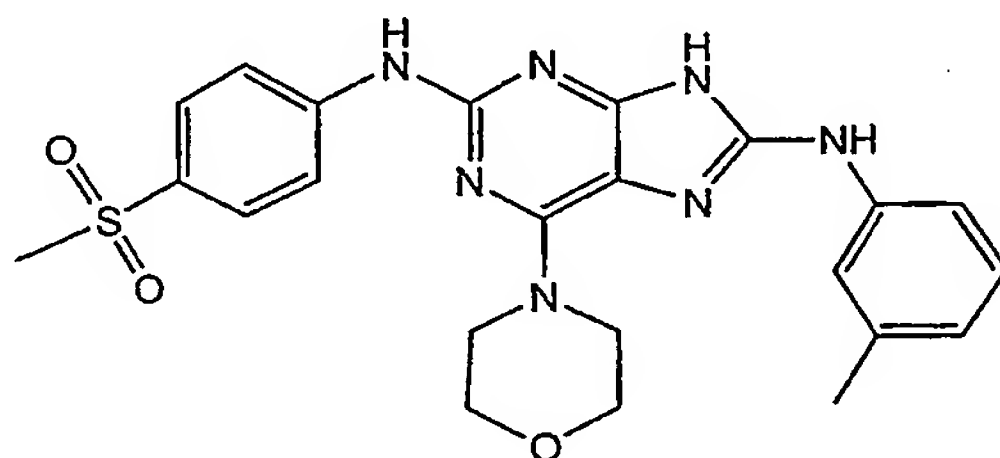
The title compound was prepared by a method as delineated herein.

^1H NMR (CD_3OD) δ (ppm), 8.68 (d, $J=8.7\text{Hz}$, 1H), 8.04 (d, $J=2.1\text{Hz}$, 1H), 7.76 (dd, $J=2.1, 8.7\text{Hz}$, 1H), 7.49 (s, 1H), 7.34 (m, 1H), 7.16 (t, $J=8.1\text{Hz}$, 1H), 6.77 (d, $J=8.1\text{Hz}$, 1H), 4.18 (m, 4H), 3.83 (m, 4H), 2.30 (s, 3H).

20

ESMS calcd for $\text{C}_{22}\text{H}_{23}\text{BrN}_8\text{O}_3\text{S}$: 558.08; Found: 559.0 ($\text{M}+\text{H}$) $^+$.

Example 34. Preparation of N^2 -(4-methanesulfonyl-phenyl)-6-morpholin-4-yl- N^8 -*m*-tolyl-9*H*-purine-2,8-diamine



5

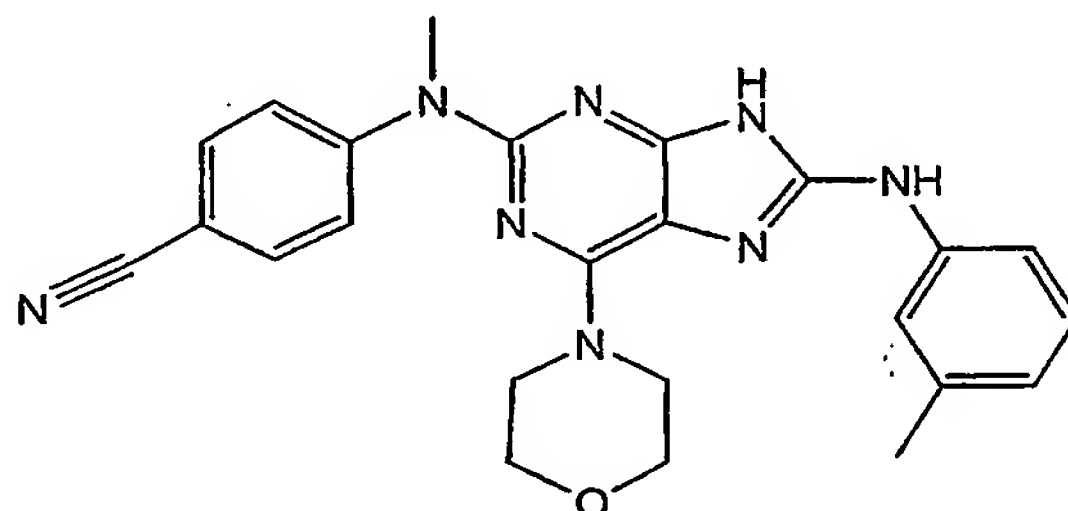
The title compound was prepared by a method as delineated herein.

$^1\text{H-NMR}$ (DMSO- d_6) δ (ppm), 9.52 (br., 1H), 9.23 (br., 1H), 7.93 (m, 2H), 7.75 (m, 2H), 7.34-7.41 (m, 2H), 7.17 (m, 1H), 6.77 (m, 1H), 4.07 (m, 4H), 3.75 (m, 4H), 3.13 (s, 3H), 2.28 (s, 3H).

10

ESMS calcd for $\text{C}_{23}\text{H}_{25}\text{N}_7\text{O}_3\text{S}$: 479.17; Found: 480.2 ($\text{M}+\text{H}$) $^+$.

Example 35. Preparation of 4-[methyl-(6-morpholin-4-yl-8-*m*-tolylamino-9*H*-purin-2-yl)-amino]-benzonitrile



15

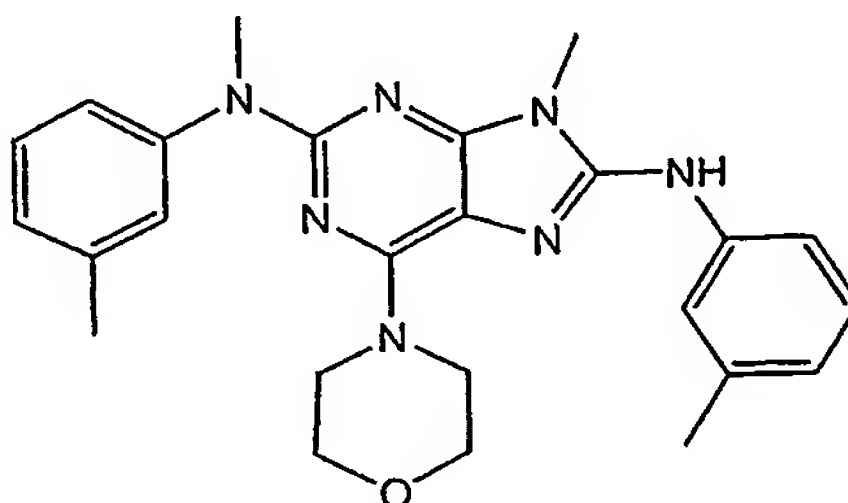
The title compound was prepared by a method as delineated herein.

$^1\text{H NMR}$ (CD_3OD) δ (ppm), 7.37-7.59 (m, 6H), 7.21 (m, 1H), 6.81 (m, 1H), 4.15 (m, 4H), 3.83 (m, 4H), 3.59 (s, 3H), 2.35 (s, 3H).

20

ESMS calcd for $\text{C}_{24}\text{H}_{24}\text{N}_8\text{O}$: 440.21; Found: 441.2 ($\text{M}+\text{H}$) $^+$.

Example 36. Preparation of N^2 -dimethyl-6-morpholin-4-yl- N^2, N^8 -di-*m*-tolyl-9*H*-purine-2,8-diamine



5

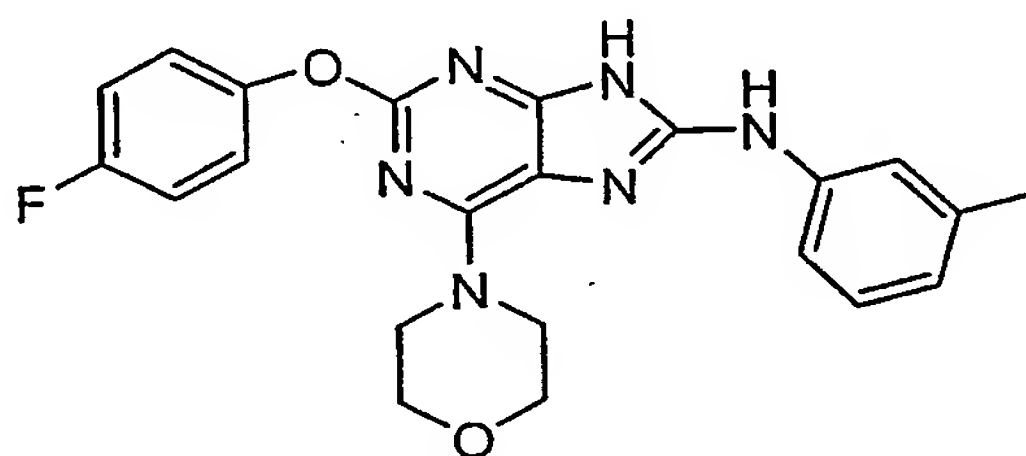
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 9.58 (br., 2H), 7.58 (m, 1H), 7.52 (s, 1H), 7.38 (s, 1H), 7.24-7.28 (m, 3H), 6.91-6.99 (m, 2H), 3.84 (s, 3H), 3.69 (m, 4H), 3.65 (s, 3H), 3.58 (m, 4H), 2.34 (s, 3H), 2.32 (s, 3H).

10

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}$: 443.24; Found: 444.2 ($\text{M}+\text{H}$) $^+$.

Example 37. Preparation of [2-(4-Fluoro-phenoxy)-6-morpholin-4-yl-9*H*-purin-8-yl]-*m*-tolyl-amine



15

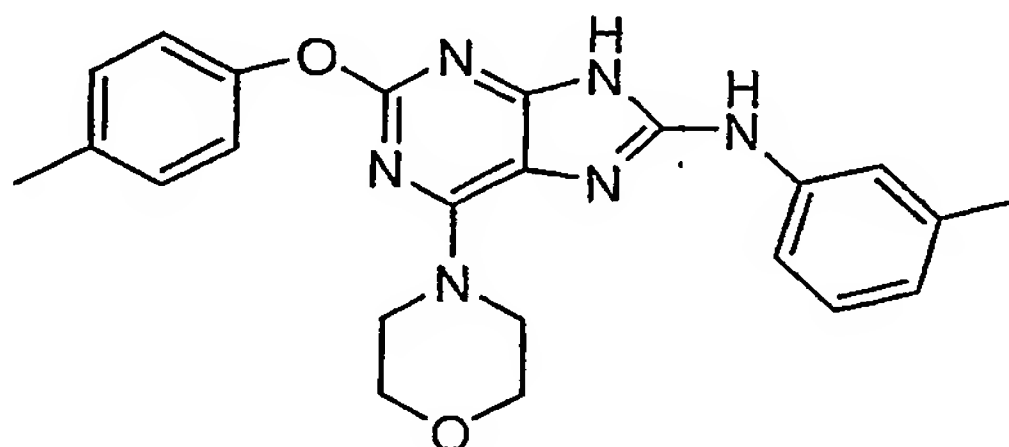
The title compound was prepared by a method as delineated herein.

^1H NMR (acetone- d_6) δ (ppm), 10.68 (s, 1H), 8.55 (s, 1H), 7.56 (s, 1H), 7.48 (d, $J=8.4$ Hz, 1H), 7.19-7.14 (m, 5H), 6.78 (d, $J=7.2$ Hz, 1H), 4.12 (m, 4H), 3.75 (m, 4H), 2.30 (s, 3H).

20

ESMS calcd for $\text{C}_{22}\text{H}_{21}\text{FN}_6\text{O}_2$: 420.17; Found: 421.1 ($\text{M}+\text{H}$) $^+$.

Example 38. Preparation of (6-morpholin-4-yl-2-*p*-tolylloxy-9*H*-purin-8-yl)-*m*-tolyl-amine



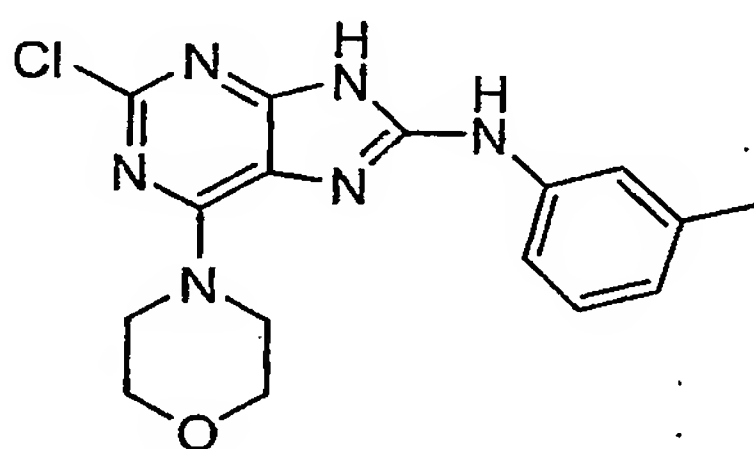
5 The title compound was prepared by a method as delineated herein.

¹H NMR (acetone-d₆) δ (ppm), 10.60 (s, 1H), 8.59 (s, 1H), 7.56 (s, 1H), 7.48 (d, *J*=9.0 Hz, 1H), 7.27-7.13 (m, 4H), 7.02 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 4.14 (m, 4H), 3.75 (m, 4H), 2.33 (s, 3H), 2.30 (s, 3H).

ESMS calcd for C₂₃H₂₄N₆O₂: 416.20; Found: 417.2 (M+H)⁺.

10

Example 39. Preparation of (2-chloro-6-morpholin-4-yl-9*H*-purin-8-yl)-*m*-tolyl-amine



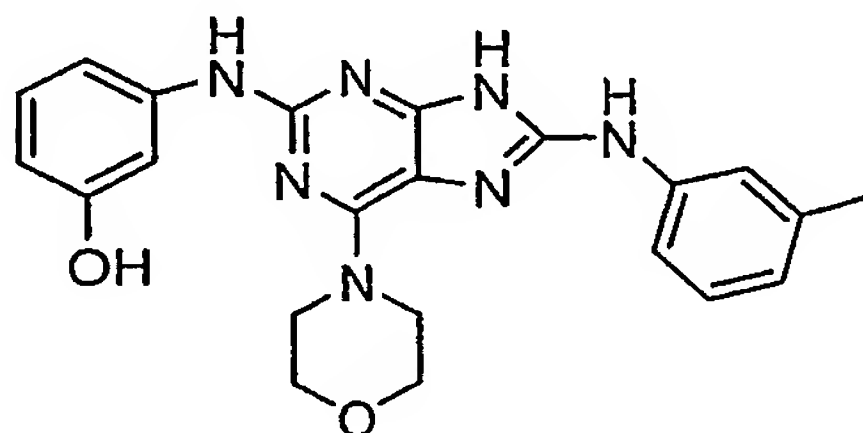
15 The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 12.00 (brs, 1H), 9.39 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J*=8.1 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 6.75 (d, *J*=7.2 Hz, 1H), 4.09 (m, 4H), 3.72 (m, 4H), 2.27 (s, 3H).

ESMS calcd for C₁₆H₁₇ClN₆O: 344.12; Found: 345.2 (M+H)⁺.

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Example 40. Preparation of 3-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-ylamino)-phenol



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The title compound was prepared by a method as delineated herein.

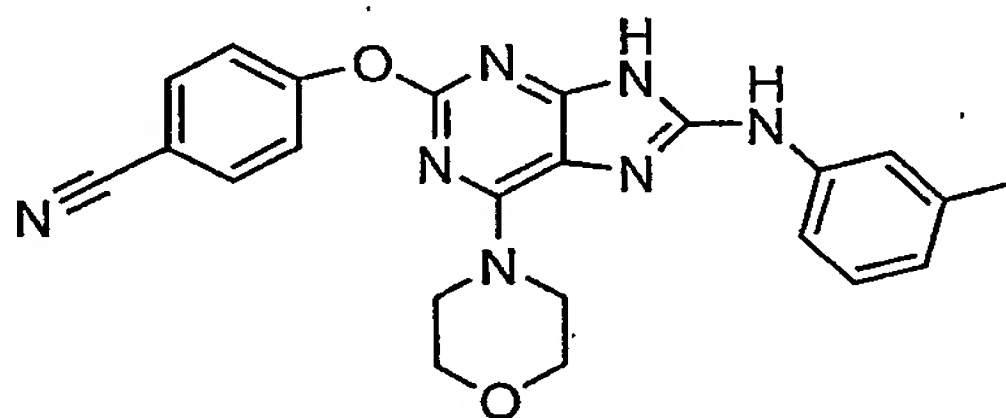
^1H NMR (acetone- d_6) δ (ppm), 10.46 (brs, 1H), 8.39 (s, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.56 (s, 1H), 7.49-7.45 (m, 2H), 7.18 (brd, $J=8.7$ Hz, 1H), 7.15 (t, $J=7.8$ Hz, 1H), 7.02 (t, $J=8.0$ Hz, 1H), 6.75 (brd, $J=6.9$ Hz, 1H), 6.37 (ddd, $J=7.4$, 2.1 and 0.8 Hz, 1H), 4.19 (m, 4H), 3.77 (m, 4H), 2.30 (s, 3H).

10

ESMS calcd for $\text{C}_{22}\text{H}_{23}\text{N}_7\text{O}_2$: 417.19; Found: 418.2 ($\text{M}+\text{H}$) $^+$.

Example 41. Preparation of 4-(6-morpholin-4-yl-8-m-tolylamino-9H-purin-2-yloxy)-benzonitrile

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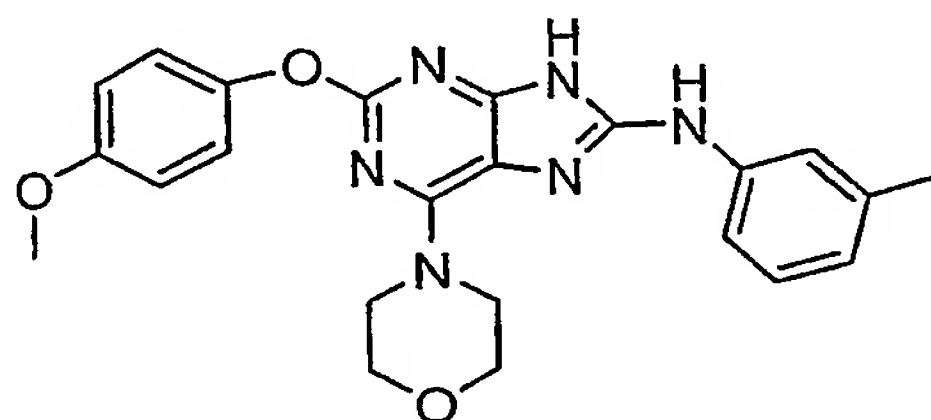
The title compound was prepared by a method as delineated herein.

^1H NMR (acetone- d_6) δ (ppm), 10.71 (brs, 1H), 8.61 (s, 1H), 7.81 (m, $J_{AA}=8.7$ Hz, 2H), 7.56 (s, 1H), 7.49 (brd, $J=7.5$ Hz, 1H), 7.36 (m, $J_{AA}=8.7$ Hz, 2H), 7.17 (t, $J=8.0$ Hz, 1H), 6.79 (d, $J=7.5$ Hz, 1H), 4.14 (m, 4H), 3.74 (m, 4H), 2.30 (s, 3H).

20

ESMS calcd for $\text{C}_{23}\text{H}_{21}\text{N}_7\text{O}_2$: 427.18; Found: 428.2 ($\text{M}+\text{H}$) $^+$.

Example 42. Preparation of [2-(4-Methoxy-phenoxy)-6-morpholin-4-yl-9H-purin-8-yl]-*m*-tolyl-amine

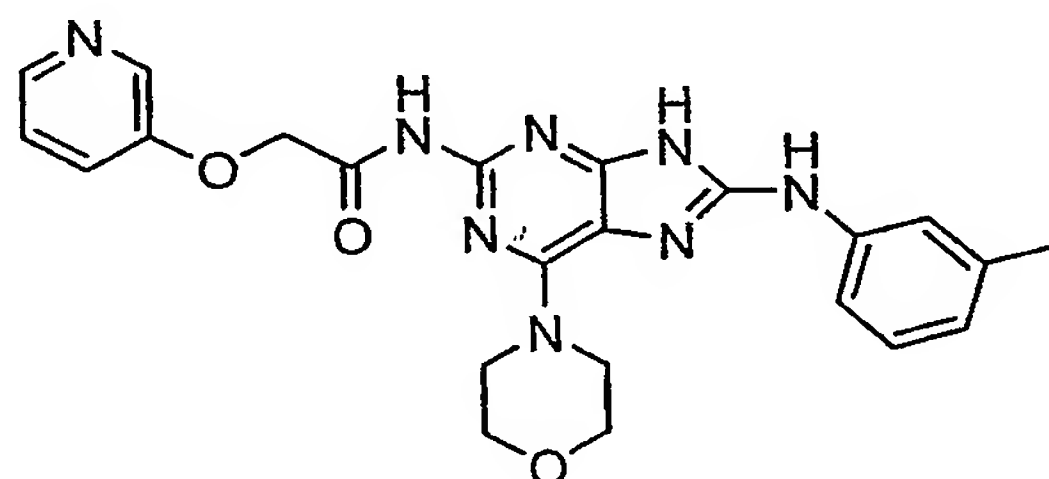


The title compound was prepared by a method as delineated herein.

¹H NMR (acetone-d₆) δ (ppm), 10.63 (brs, 1H), 8.54 (s, 1H), 7.55 (s, 1H), 7.48 (brd, *J*=9.0 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 7.07 (m, *J*_{AA}=9 Hz, 2H), 6.93 (m, *J*_{BB}=9.3 Hz, 2H), 6.76 (d, *J*=7.2 Hz, 1H), 4.12 (m, 4H), 3.80 (s, 3H), 3.75 (m, 4H), 2.29 (s, 3H).

ESMS calcd for C₂₃H₂₄N₆O₃: 432.19; Found: 433.2 (M+H)⁺.

Example 43. Preparation of N-(6-morpholin-4-yl-8-*m*-tolylamino-9H-purin-2-yl)-2-(pyridin-3-yloxy)-acetamide

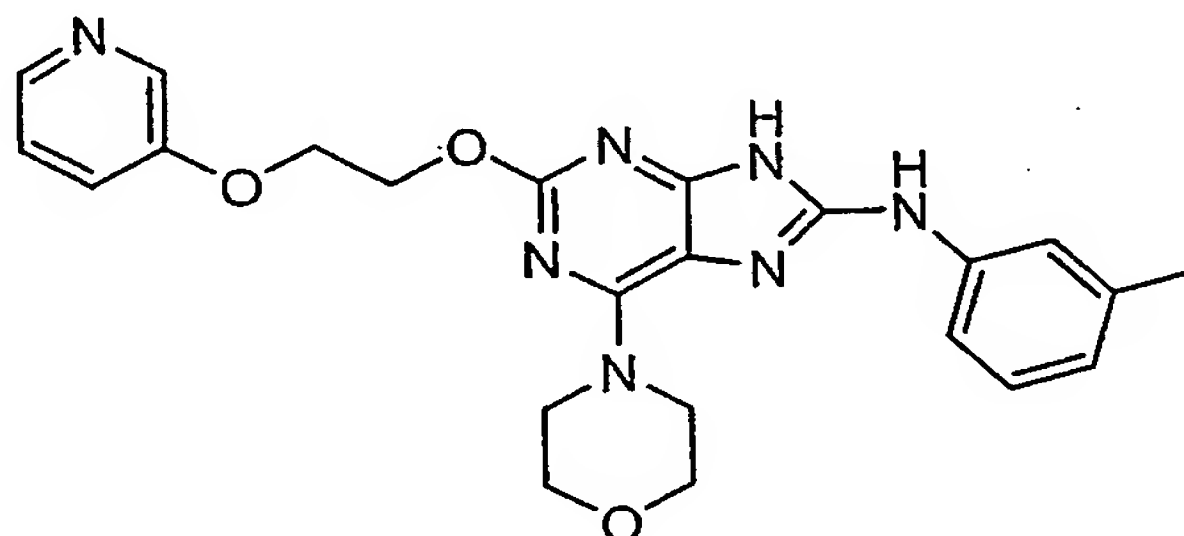


The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-d₆) δ (ppm), 10.08 (s, 1H), 9.2 (s, 1H), 8.31 (s, 1H), 8.18 (m, 1H), 7.46-7.35 (m, 4H), 7.15 (t, *J*=7.6 Hz, 1H), 6.73 (d, *J*=8.1 Hz, 1H), 5.10 (s, 2H), 4.11 (m, 4H), 3.73 (m, 4H), 2.27 (s, 3H).

ESMS calcd for C₂₃H₂₄N₈O₃: 460.20; Found: 461.2 (M+H)⁺.

Example 44. Preparation of {6-morpholin-4-yl-2-[2-(pyridin-3-yloxy)-ethoxy]-9H-purin-8-yl]-*m*-tolyl-amine



5

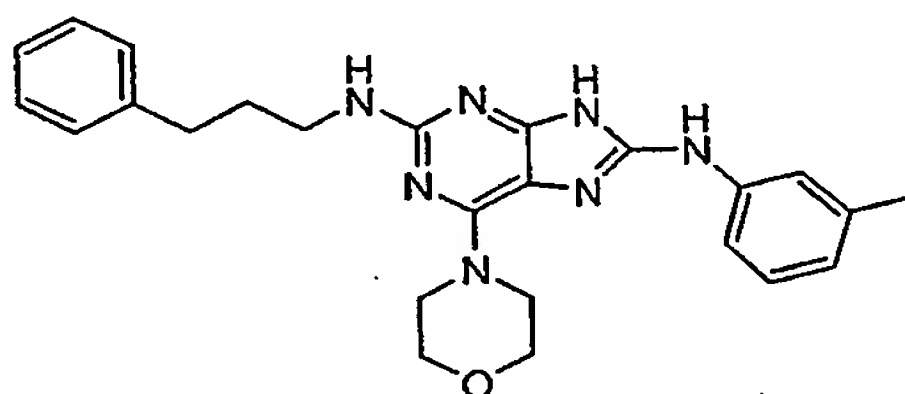
The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 11.75 (s, 1H), 9.12 (s, 1H), 8.34 (s, 1H), 8.19 (d, $J=4.3$ Hz, 1H), 7.46-7.35 (m, 4H), 7.17 (t, $J=7.6$ Hz, 1H), 6.71 (d, $J=8.1$ Hz, 1H), 4.54 (m, 2H), 4.38 (m, 2H), 4.08 (m, 4H), 3.71 (m, 4H), 2.27 (s, 3H).

10

ESMS calcd for $\text{C}_{23}\text{H}_{25}\text{N}_7\text{O}_3$: 447.20; Found: 448.5 ($\text{M}+\text{H}$) $^+$.

Example 45. Preparation of 6-morpholin-4-yl- N^2 -(3-phenyl-propyl)- N^8 -*m*-tolyl-9H-purine-2,8-diamine



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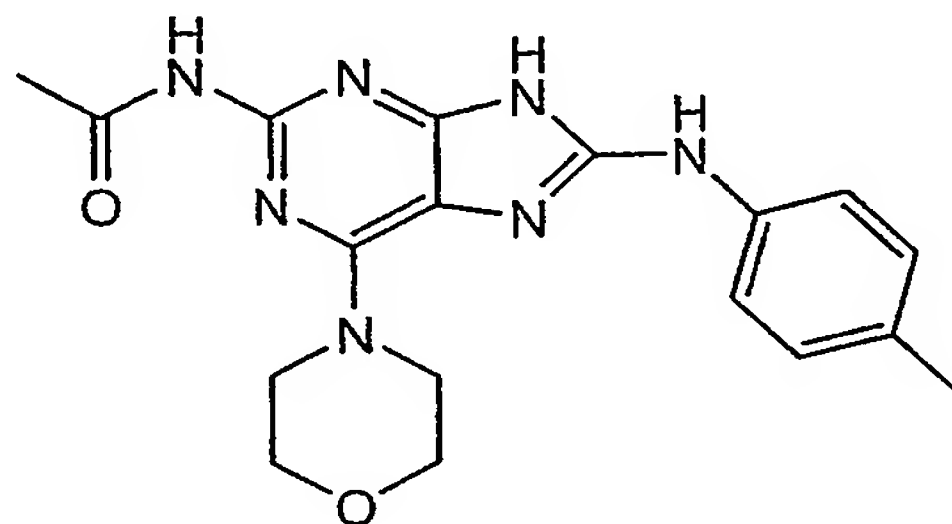
The title compound was prepared by a method as delineated herein.

^1H NMR (acetone- d_6) δ (ppm), 8.34 (brs, 1H), 7.52-7.14 (m, 9H), 6.71 (s, 1H), 5.63 (brs, 1H), 4.11 (m, 4H), 3.73 (m, 4H), 3.38 (m, 2H), 2.67 (t, $J=7.8$ Hz, 2H), 2.25 (s, 3H), 1.90 (qv, $J=7.5$ Hz, 2H).

20

ESMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}$: 443.24; Found: 444.2 ($\text{M}+\text{H}$) $^+$.

Example 46. Preparation of N-(6-morpholin-4-yl-8-*p*-tolylamino-7*H*-purin-2-yl)-acetamide



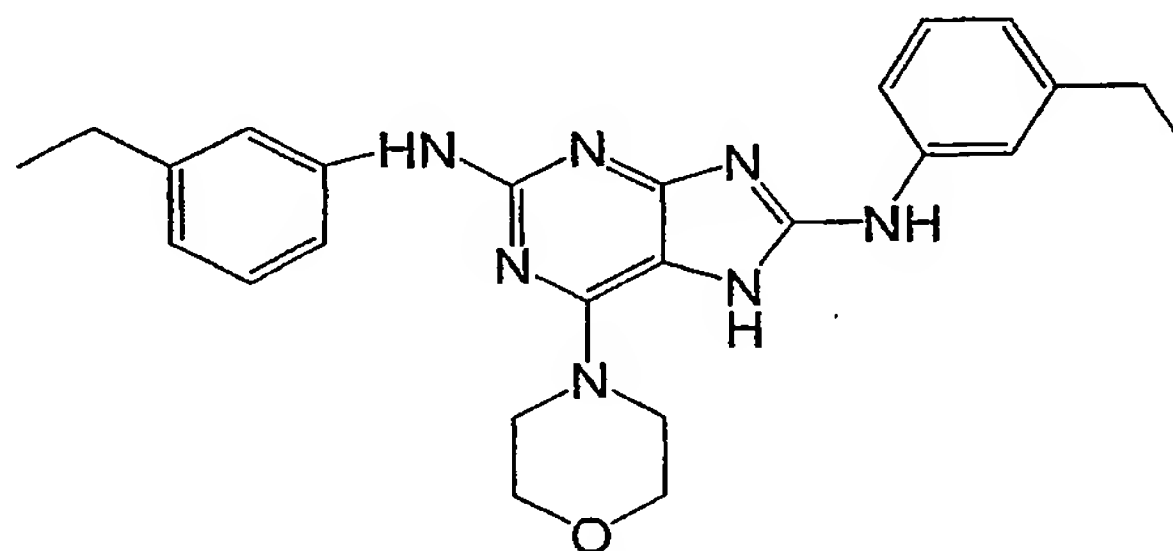
5 The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-*d*₆) δ (ppm), 11.79 (brs, 1H), 9.77 (s, 1H), 9.14 (s, 1H), 7.49 (d, *J*=7.8 Hz, 2H), 7.08 (d, *J*=7.8 Hz, 2H), 4.09 (m, 4H), 3.71 (m, 4H), 2.24 (s, 3H), 2.16 (s, 3H).

ESMS calcd for C₁₈H₂₁N₇O₂: 367.18; Found: 368.2 (M+H)⁺.

10

Example 47. Preparation of N-2',N-8'-Bis-(3-ethyl-phenyl)-6-morpholin-4-yl-7*H*-purine-2,8-diamine



15

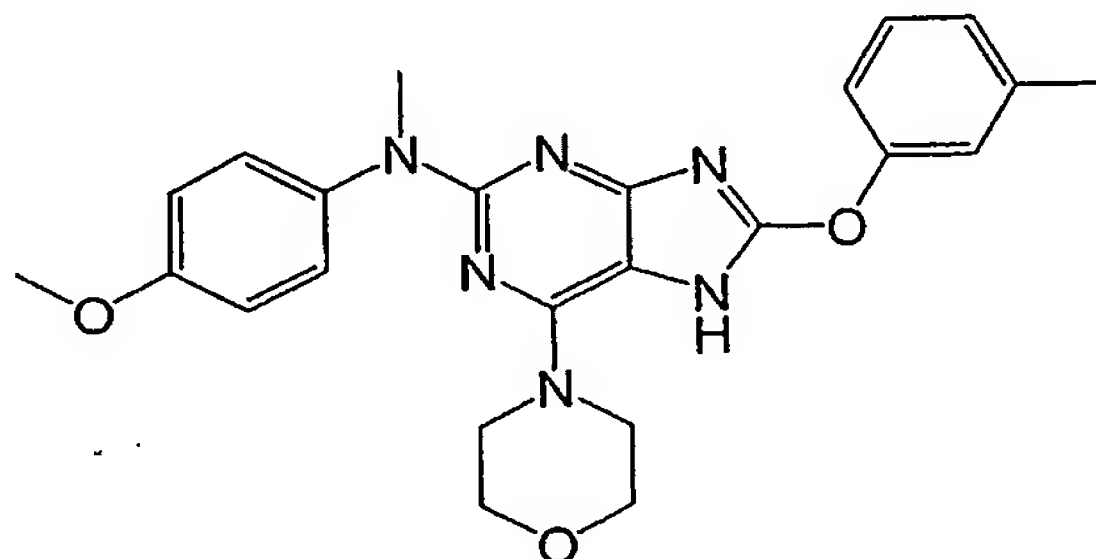
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-*d*₆) δ (ppm), 9.43 (s, 1H), 7.63 (s, 1H), 7.31 (d, *J*=8.7 Hz, 1H), 7.18 (dd, *J*₁=8.7 Hz, *J*₂=6.9 Hz, 1H), 6.78 (d, *J*=6.9 Hz), 4.11 (bs, 4H), 3.72 (bs, 4H), 2.58 (q, *J*=7.5 Hz, 2H), 1.18 (t, *J*=7.5 Hz, 3H).

20

ESMS calcd for C₂₅H₂₉N₇O: 443.24; Found: 444.1 (M+H)⁺.

Example 48. Preparation of (4-methoxy-phenyl)-methyl-(6-morpholin-4-yl-8-m-tolyloxy-7H-purin-2-yl)-amine



5

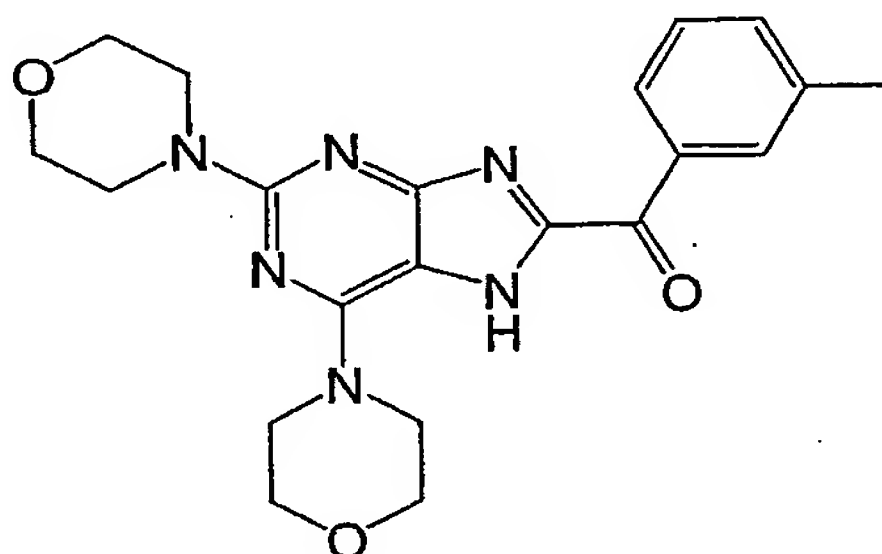
The title compound was prepared by a method as delineated herein.

^1H NMR (CDCl_3) δ (ppm), 7.26-7.21 (m, 3H), 7.07-7.04 (m, 2H), 6.97 (d, $J=7.2$ Hz, 1H), 4.02 (bs, 4H), 3.78 (s, 3H), 3.73 (m, 4H), 3.49 (s, 3H), 3.32 (s, 3H).

ESMS calcd for $\text{C}_{24}\text{H}_{26}\text{N}_6\text{O}_3$: 446.21; Found: 447.1 ($\text{M}+\text{H}$) $^+$.

10

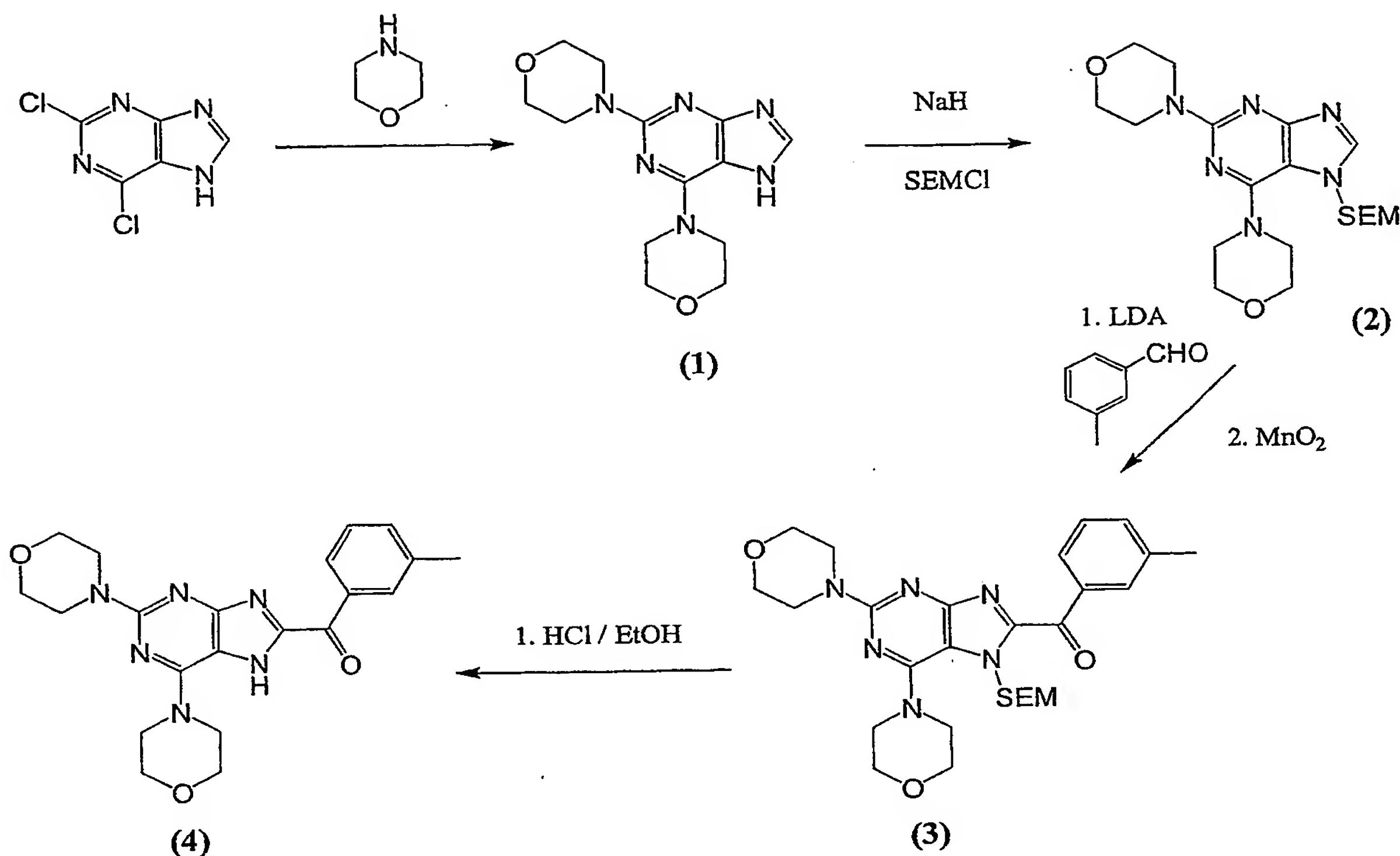
Example 49. Preparation of (2,6-di-morpholin-4-yl-7H-purin-8-yl)-*m*-tolyl-methanone



15

The title compound was synthesized by the method shown in Scheme 5.

Scheme 5



As shown in Scheme 5 above, 2,6-dichloropyrimidine (1 g, 5.29 mmol) was dissolved in morpholine (5 mL) in a sealed tube. The tube was heated to 120°C for 5 hours then cooled to room temperature. Water (100 mL) was added and the resulting precipitate was filtered and washed with water to give 2,6-di-morpholin-4-yl-7H-purine (1.33 g, 87%). 2,6-Di-morpholin-4-yl-7H-purine (1.33 g, 4.58 mmol) was dissolved in DMF (50 mL). NaH (0.22 g, 5.50 mmol, 60% dispersion in oil) was added and the reaction was stirred at room temperature for 30 min. 2-(Trimethylsilyl)ethoxymethyl chloride (0.92 g, 5.50 mmol) was added dropwisely and the reaction was stirred for 18 h at room temperature. Water (200 mL) then ethyl acetate (200 mL) were added. The ethyl acetate extracts were washed with water (3x100 mL), dried over MgSO₄, filtered and evaporated to dryness. The resulting residue was purified by silicagel column chromatography eluting with a gradient of 1:1 ethyl acetate to ethyl acetate to produce 2,6-Di-morpholin-4-yl-7-(2-trimethylsilanylethoxymethyl)-7H-purine (1.51 g, 78% yield).

^1H NMR ($\text{DMSO}-d_6$) δ (ppm), 8.23 (s, 1H), 8.18 (d, $J=7.1$ Hz, 1H), 7.22-7.18 (m, 4H), 6.97 (d, $J=9.3$ Hz, 2H), 5.78 (s, 1H), 4.15 (bs, 4H), 3.80-3.78 (m, 7H), 3.43 (s, 3H), 2.33 (s, 3H).

ESMS calcd for $\text{C}_{19}\text{H}_{32}\text{N}_6\text{O}_3\text{Si}$: 420.23; Found: 421.2 ($\text{M}+\text{H}$) $^+$.

5 2,6-Di-morpholin-4-yl-7-(2-trimethylsilanylethoxymethyl)-7H-purine (266 mg, 0.63 mmol) was dissolved in dry THF (10 mL) and cooled to -78°C . A solution of LDA (0.38 mL, 0.76 mmol, 2 M solution in heptane) was added dropwisely then the reaction was stirred at -78°C for 30 min. To the resulting suspension was added a solution of *m*-tolylaldehyde (114 mg, 0.95 mmol) in THF (5 mL) then the reaction
10 was stirred for 1 hour. Saturated NH_4Cl (50 mL) was added then the reaction was allowed to warm to room temperature. THF was removed under reduced pressure then ethyl acetate (50 mL) was added. The ethyl acetate layer was washed with water (3 x 50 mL), dried over MgSO_4 then evaporated to dryness. The crude product was purified by silcagel column chromatography. Elution with 25% ethyl acetate/hexane
15 produced [2,6-di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-purin-8-yl]-*m*-tolyl-methanone (198 mg, 56% yield).

^1H NMR (CDCl_3) δ (ppm), 8.11 (s, 1H), 8.07 (d, $J=7.2$ Hz, 1H), 7.40-7.39 (m, 2H), 5.95 (s, 2H), 3.84-3.78 (m, 16H), 3.68-3.63 (m, 2H), 2.43 (s, 3H), 0.97-0.91 (m, 2H), -0.08 (s, 9H).

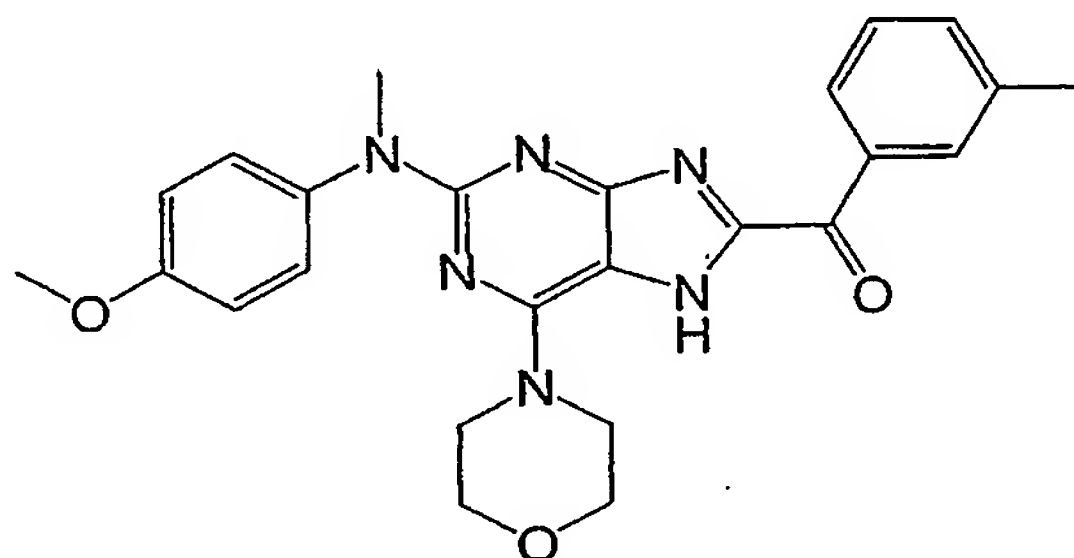
20 ESMS calcd for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_4\text{Si}$: 538.27; Found: 539.2 ($\text{M}+\text{H}$) $^+$.

[2,6-Di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-purin-8-yl]-*m*-tolyl-methanone (185 mg, 0.34 mmol) was dissolved in ethanol (10 ml) and 2N HCl (4 mL). The resulting suspension was heated to reflux for 4 hrs then cooled to room temperature. After neutralization with 2N NaOH, ethanol was removed under
25 reduced pressure and ethyl acetate (100 mL) was added. The ethyl acetate layer was washed with water (3x50 mL), dried over MgSO_4 then evaporated to dryness. The crude product was purified by silcagel column chromatography. Elution with a gradient of 25% ethyl acetate/hexane to ethyl acetate to 10 % methanol/ethyl acetate produced (2,6-di-morpholin-4-yl-7H-purin-8-yl)-*m*-tolyl-methanone (80 mg, 57 %
30 yield).

^1H NMR ($\text{DMSO}-d_6$) δ (ppm), 8.34 (s, 1H), 8.28 (d, $J=7.5$ Hz, 1H), 7.62-7.58 (m, 2H), 3.89-3.80 (m, 16H), 2.54 (s, 3H).

ESMS calcd for $C_{21}H_{24}N_6O_3$: 408.19; Found: 409.1 (M+H)⁺.

Example 50. Preparation of {2-[(4-Methoxy-phenyl)-methyl-amino]-6-morpholin-4-yl-7H-purin-8-yl}-*m*-tolyl-methanone



5

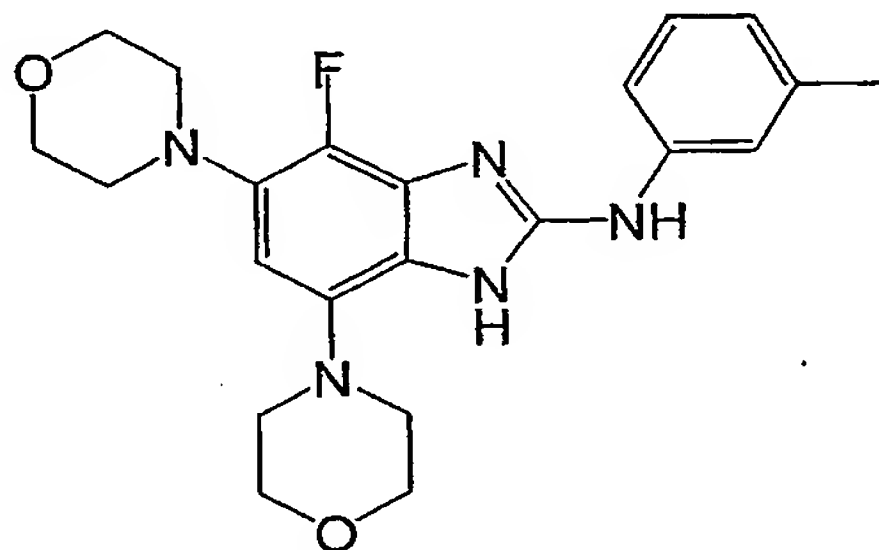
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-*d*₆) δ (ppm), 8.19 (s, 1H), 8.12 (d, *J*=7.5 Hz, 1H), 7.46-7.43 (m, 2H), 7.25 (d, *J*=9.3 Hz, 2H), 6.93 (d, *J*=9.3 Hz, 2H), 4.04 (bs, 4H), 3.77 (s, 3H), 3.70 (bs, 4H), 3.43 (s, 3H), 2.39 (s, 3H).

10

ESMS calcd for $C_{25}H_{26}N_6O_3$: 458.21; Found: 459.1 (M+H)⁺.

Example 51. Preparation of (4-fluoro-5,7-di-morpholin-4-yl-1H-s-yl)-*m*-tolyl-amine



15

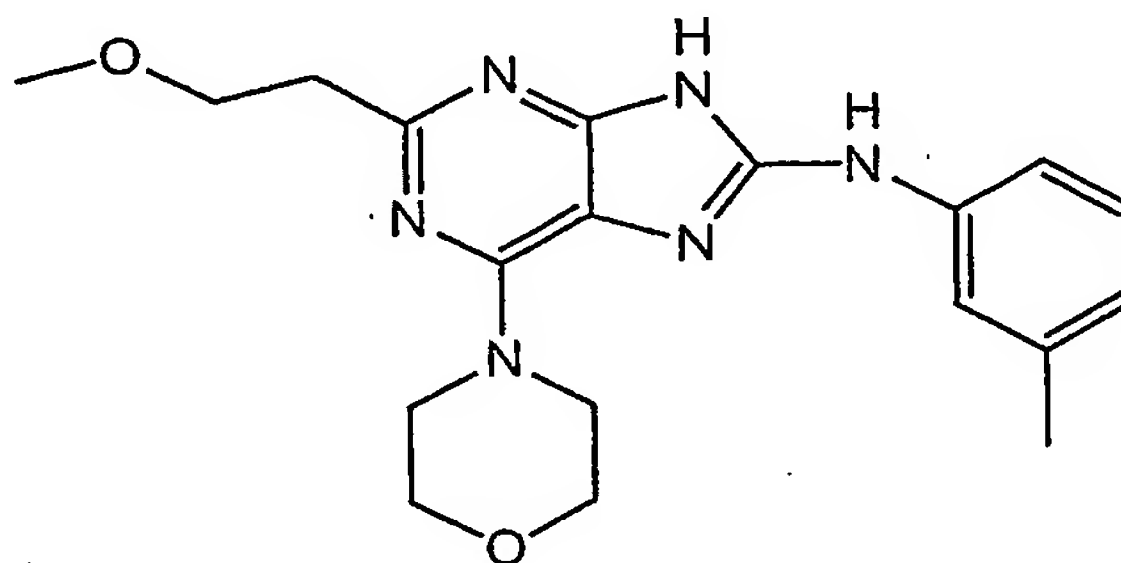
The title compound was prepared by a method as delineated herein.

¹H NMR (DMSO-*d*₆) δ (ppm), 7.5- 7.1 (m, 5H), 3.89-3.80 (m, 16H), 2.54 (s, 3H),

ESMS calcd for $C_{22}H_{26}FN_5O_2$: 411.2; Found: 412.1 (M+H)⁺.

20

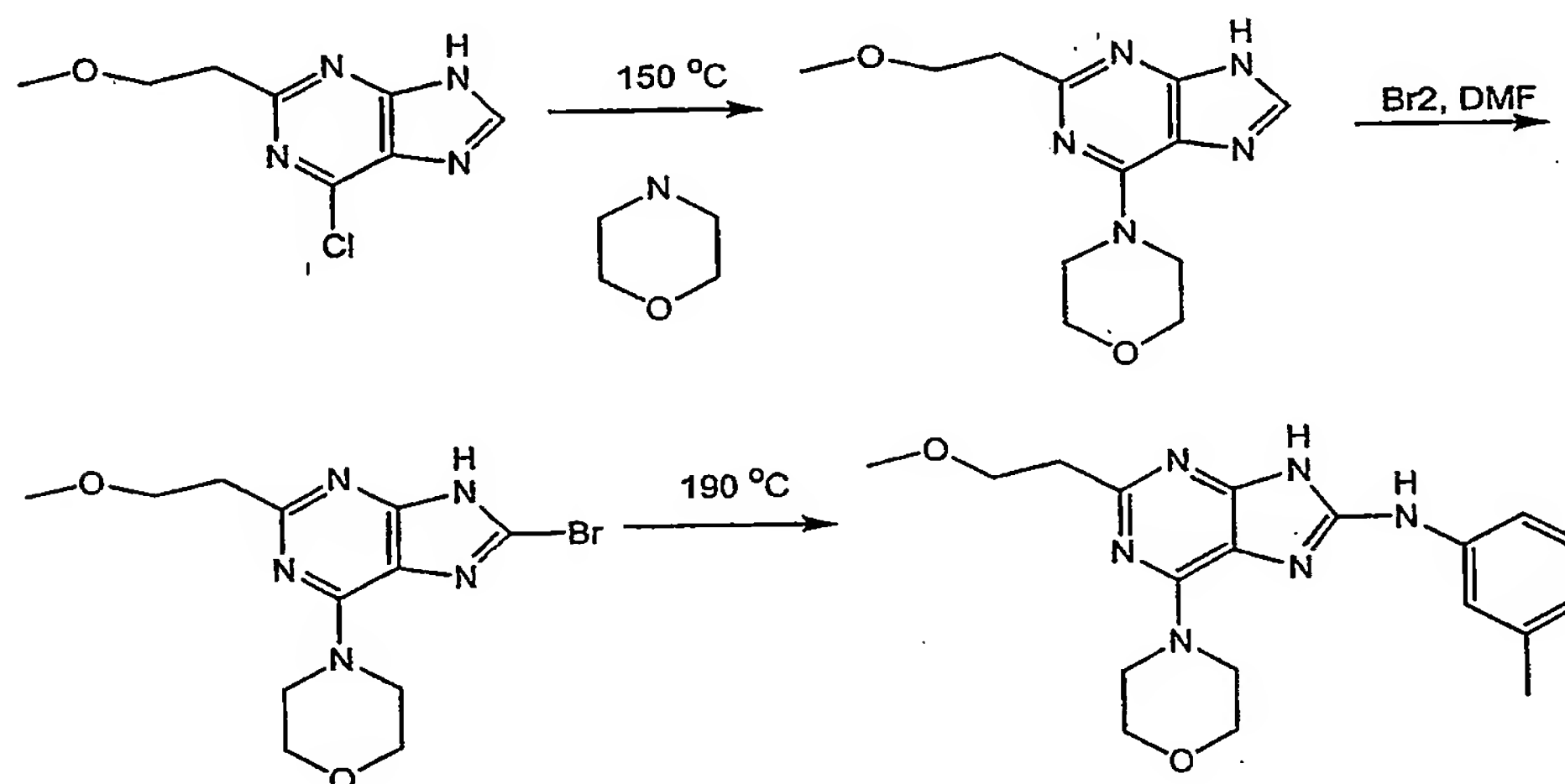
Example 52. Preparation of [2-(2-methoxy-ethyl)-6-morpholin-4-yl-9H-purin-8-yl]-*m*-tolyl-amine



5

The title compound was prepared by the method shown in Scheme 6.

Scheme 6



10

6-Chloro-2-(2-methoxy-ethyl)-9H-purine (0.5 g, 2.4 mmol, synthesized by following the procedure reported by Crespo and al. (*Journal of Medicinal Chemistry*, 1998, Vol. 41, No. 21, p. 4024) was heated in morpholine (1 mL, 5 eq) at 150°C for 15 minutes. Reaction mixture was cooled to room temperature and distributed between dichloromethane and water. Organic layer was washed 2 times with water, then with brine, dried over MgSO₄ and 2-(2-methoxy-ethyl)-6-morpholin-4-yl-9H-purine (0.46 g, 75%) was isolated by column chromatography.

15

ESMS calcd for C₁₂H₁₇N₅O₂: 263.14; Found: 286.2 (M+23)⁺.

To a solution of 2-(2-methoxy-ethyl)-6-morpholin-4-yl-9H-purine (0.46 g, 1.7 mmol) in 1 mL of DMF bromine (0.34 g, 1.2 eq) was added dropwise, and a

resulted solution was heated at 110°C for 30 minutes. Solvent was removed in vacuo, a residue was dissolved in dichloromethane, washed with water, brine and dried over MgSO₄. Residue was purified by passing through silica gel (eluent dichloromethane:acetone:methanol 3:1:0.25) to afford 8-bromo-2-(2-methoxy-ethyl) – 6-morpholin-4-yl-9H-purine (0.42 g, 70%).

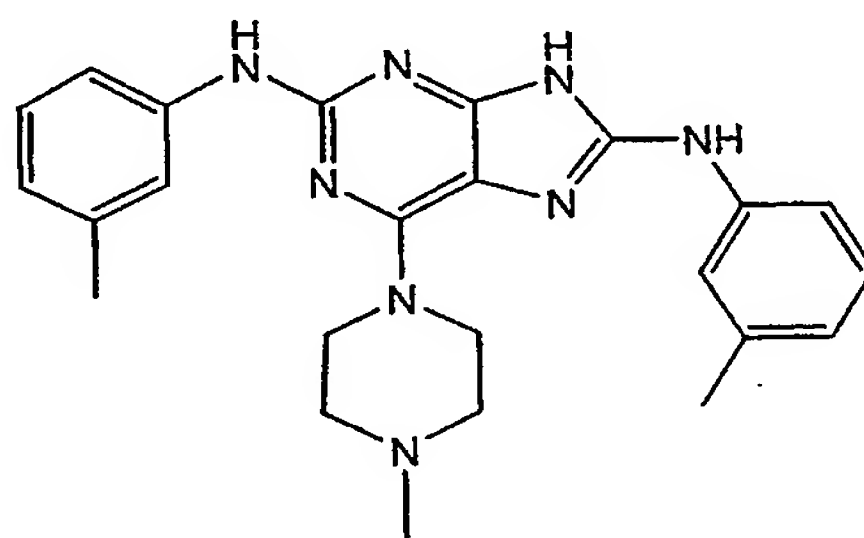
ESMS calcd for C₁₂H₁₆BrN₅O₂: 341.05; Found: 342.0 (M+1)⁺.

A suspension of 8-bromo-2-(2-methoxy-ethyl) – 6-morpholin-4-yl-9H-purine (0.42 g, 1.2 mmol) in *m*-toluidine (0.5 mL, 3.8 eq) in a tightly stoppered flask was heated at 190°C for 15 minutes. Column chromatography afforded [2-(2-methoxy-ethyl)-6-morpholin-4-yl-9H-purin-8-yl]-*m*-tolyl-amine (0.36 g, 81%) as an off-white solid.

¹H NMR (DMSO-d₆): δ 11.70 (s, 1H), 9.24 (s, 1H), 7.47 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 4.11 (m, 4H), 3.75 (t, *J* = 6.9 Hz, 2H), 3.73 (m, 4H), 3.24 (s, 3H), 2.88 (t, *J* = 6.9 Hz, 2H), 2.27 (s, 3H).

ESMS calcd for C₁₉H₂₄N₆O₂: 368.20; Found: 369.1 (M+1)⁺.

Example 53. Preparation of *N*², *N*⁸-bis-(3-methylphenyl)-6-(4-methylpiperidinyl)-9H-purine-2,8-diamine

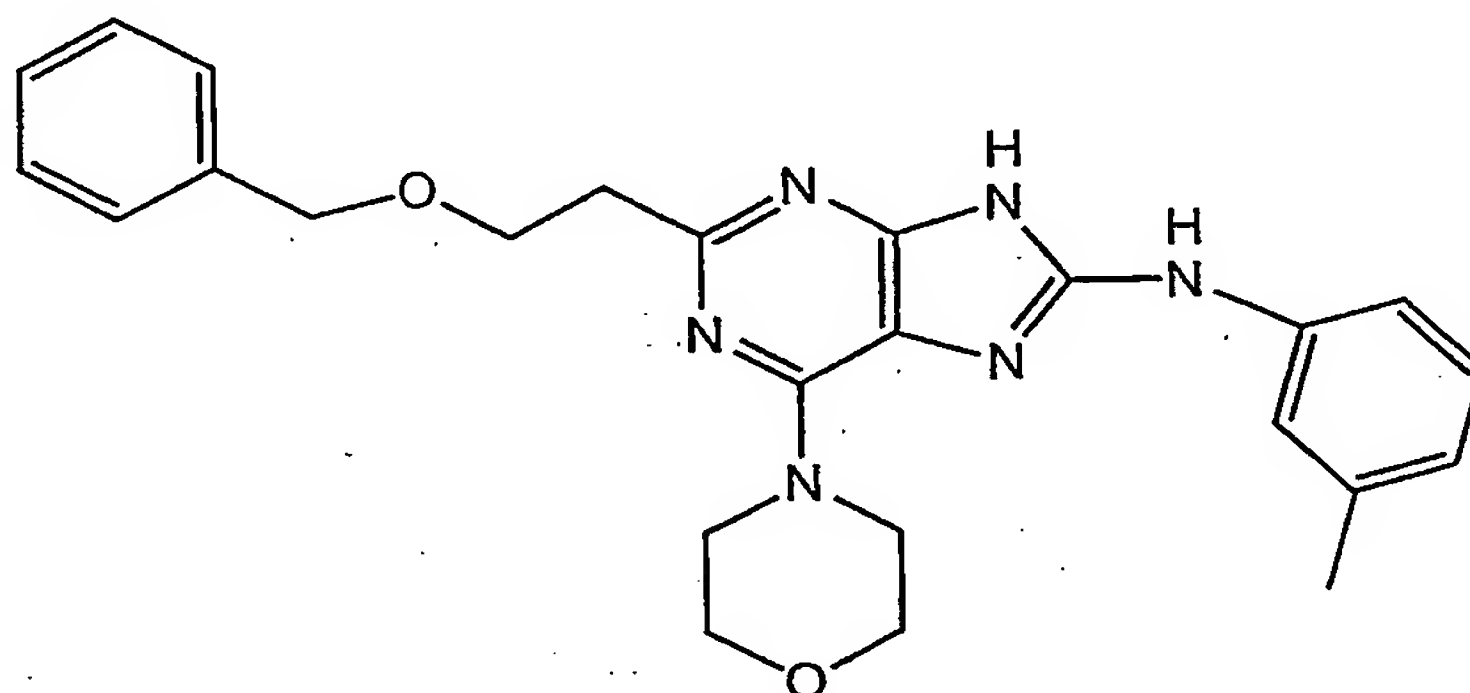


The title compound was prepared by a method as delineated herein.

¹H NMR (CD₃OD) δ (ppm), 7.4-7.1 (m, 6H), 6.77-6.82 (m, 2H), 4-3.5 (m, 11H), 2.30 (m, 6H).

ESMS calcd for C₂₄H₂₈N₈: 428.24; Found: 429.2 (M+H)⁺.

Example 54. Preparation of [2-(2-Benzoyloxy-ethyl)-6-morpholin-4-yl-9H-purin-8-yl]-*m*-tolyl-amine

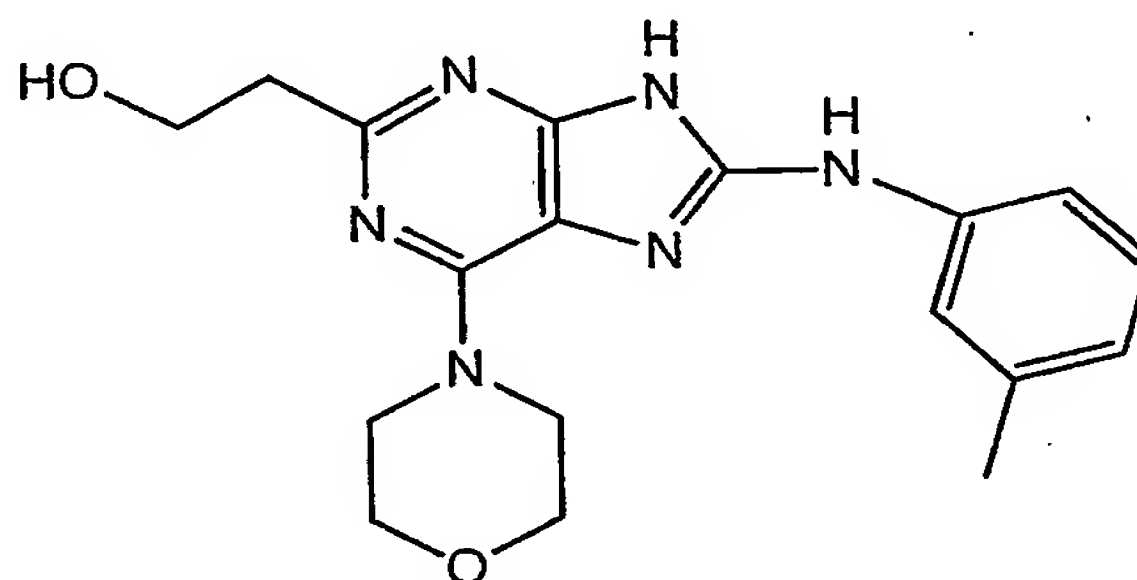


The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 11.70 (s, 1H), 9.24 (s, 1H), 7.47 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.32-7.26 (m, 5H), 7.14 (t, $J = 8.0$ Hz, 1H), 6.72 (d, $J = 7.5$ Hz, 1H), 4.49 (s, 2H), 4.10 (m, 4H), 3.86 (t, $J = 6.9$ Hz, 2H), 3.71 (m, 4H), 2.94 (t, $J = 6.9$ Hz, 2H), 2.27 (s, 3H).

ESMS calcd for $\text{C}_{25}\text{H}_{28}\text{N}_6\text{O}_2$: 444.23; Found: 445.3 ($\text{M}+\text{H}$) $^+$.

Example 55. Preparation of 2-(6-Morpholin-4-yl-8-*m*-tolylamino-9H-purin-2-yl)-ethanol



The title compound was prepared by a method as delineated herein.

^1H NMR (DMSO- d_6) δ (ppm), 11.72 (s, 1H), 9.23 (s, 1H), 7.47 (s, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 6.72 (d, $J = 6.0$ Hz, 1H), 4.56 (s, 1H), 4.11 (m, 4H), 3.80 (m, 2H), 3.77 (m, 4H), 2.81 (m, 2H), 2.27 (s, 3H).

ESMS calcd for $\text{C}_{18}\text{H}_{22}\text{N}_6\text{O}_2$: 354.18; Found: 355.2 ($\text{M}+\text{H}$) $^+$.

Example 56. In vitro assays

Reagents. *Staphylococcus aureus* Cowan I (SAC) was obtained from Calbiochem (La Jolla, CA), and lipopolysaccharide (LPS, *Serratia marscencens*) was obtained from Sigma (St. Louis, MO). Human and mouse recombinant IFN γ were purchased from Boehringer Mannheim (Mannheim, Germany) and Pharmingen (San Diego, CA), respectively.

Human In Vitro Assay. Human PBMC were isolated by centrifugation using Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden) and prepared in RPMI medium supplemented with 10% fetal calf serum (FCS), 100 U/mL penicillin, and 100 μ g/mL streptomycin. PBMC were plated in wells of a 96-well plate at a concentration of 5×10^5 cells/well, and primed by adding IFN γ (30 U/mL) for 22 h and stimulated by adding LPS (1 μ g/mL), or by adding IFN γ (100 U/mL) and then stimulated by adding SAC (0.01%). A test compound was dissolved in DMSO, and added to wells of the 96-well plate. The final DMSO concentration was adjusted to 0.25% in all cultures, including the compound-free control. Human THP-1 cells were plated in wells, primed by adding IFN γ (100 U/mL) for 22 h and stimulated by adding SAC (0.025%) in the presence of different concentrations of the test compound. Cell-free supernatants were taken 18 h later for measurement of cytokines. Cell viability was assessed using the bio-reduction of MTS. Cell survival was estimated by determining the ratio of the absorbance in compound-treated groups versus compound-free control.

The supernatant was assayed for the amount of IL-12p40, IL-12p70, or IL-10 by using a sandwich ELISA with anti-human antibodies, i.e., a Human IL-12 p40 ELISA kit from R&D Systems (Berkeley, CA), and a Human IL-12 p70 or IL-10 ELISA kit from Endogen (Cambridge, MA). Assays were based on the manufacturer's instructions.

Murine In Vitro Assay. Balb/c mice (Taconic, Germantown, NY) were immunized with *Mycobacterium tuberculosis* H37Ra (Difco, Detroit, MI). The splenocytes were harvested 5 days and prepared in RPMI medium supplemented with 10% FCS and antibiotics in a flat bottom 96-well plate with 1×10^6 cells/well. The splenocytes were then stimulated with a combination of IFN γ (60 ng/mL) and SAC

(0.025%) [or LPS (20 µg/mL)] in the presence of a test compound. Cell-free supernatants were taken 24 h later for the measurement of cytokines. The preparation of compound and the assessment of cell viability were carried out as described above. Mouse IL-12 p70, IL-10, IL-1β, and TNFα were measured using ELISA kits from Endogen, according to the manufacturer's instructions.

The biological activities of compounds delineated herein were tested on human PBMC or THP-1 cells. All of the test compounds are active. Unexpectedly, some of the test compounds have IC₅₀ values as low as < 1 nM.

10 Example 57. In vivo assays

Treatment of adjuvant arthritis in rats: Adjuvant arthritis (AA) was induced in female Lewis rats by the intracutaneous injection (base of the tail) of 0.1 mL of a 10 mg/mL bacterial suspension made from ground, heat-killed *Mycobacterium tuberculosis* H37Ra suspended in incomplete Freund's adjuvant. Rats were given a test compound orally once a day for 12 days, starting the day following the induction. The development of polyarthritis was monitored daily by macroscopic inspection and assignment of an arthritis index to each animal, during the critical period (days 10 to 25 post-immunization).

The intensity of polyarthritis was scored according to the following scheme:

20 (a) Grade each paw from 0 to 3 based on erythema, swelling, and deformity of the joints: 0 for no erythema or swelling; 0.5 if swelling is detectable in at least one joint; 1 for mild swelling and erythema; 2 for swelling and erythema of both tarsus and carpus; and 3 for ankylosis and bony deformity. Maximum score for all 4 paws was thus 12. (b) Grade for other parts of the body: for each ear, 0.5 for redness and
25 another 0.5 if knots are present; 1 for connective tissue swelling (saddle nose); and 1 for the presence of knots or kinks in the tail. The highest possible arthritic index was 16.

Experiments with the AA model were repeated four times. Oral administration of compounds delineated herein reproducibly reduced the arthritic
30 score and delayed the development of polyarthritis. The arthritis score used in this model was a reflection of the inflammatory state of the structures monitored and the

results therefore show the ability of the test compound to provide relief for this aspect of the pathology.

Treatment of Crohn's disease in dinitrobenzene sulfonic acid-induced inflammatory bowel syndrome model rats: Wistar derived male or female rats weighing 200 ± 20 g and fasted for 24 hours were used. Distal colitis was induced by intra-colonic instillation of 2,4-dinitrobenzene sulfonic acid (DNBS, 25 mg in 0.5 mL ethanol 30%) after which air (2 mL) was gently injected through the cannula to ensure that the solution remained in the colon. A test compound and/or vehicle was administered orally 24 and 2 hours before DNBS instillation and then daily for 5 days. One control group was similarly treated with vehicle alone while the other is treated with vehicle plus DNBS. The animals were sacrificed 24 hours after the final dose of test compound administration and each colon was removed and weighed. Colon-to-body weight ratio was then calculated for each animal according to the formula: $\text{Colon (g)/BW} \times 100$. The "Net" increase in ratio of Vehicle-control + DNBS group relative to Vehicle-control group was used as a base for comparison with test substance treated groups and expressed as "% Deduction." The compounds of this invention had more than 50% reduction. A 30% or more reduction in colon-to-body weight ratio, relative to the vehicle treated control group, was considered significant.

Treatment of Crohn's disease in $CD4^+CD45Rb^{high}$ T cell-reconstituted SCID colitis model mice: Spleen cells were prepared from normal female BALB/c mice. For cell purification, the following anti-mouse antibodies were used to label non- $CD4^+$ T cells: B220 (RA3-6B2), CD11b (M1/70), and CD8 α (53-6.72). All antibodies were obtained from BioSource (Camarillo, CA). M450 anti-rat IgG-coated magnetic beads (Dynal, Oslo, Norway) were used to bind the antibodies and negative selection was accomplished using an MPC-1 magnetic concentrator. The enriched $CD4^+$ cells were then labeled for cell sorting with FITC-conjugated CD45RB (16A, Pharmingen, San Diego, CA) and PE-conjugated CD4 (CT-CD4, Caltag, Burlingame, CA). $CD4^+CD45Rb^{high}$ cells were operationally defined as the upper 40% of CD45Rb-staining $CD4^+$ cells and sorted under sterile conditions by flow cytometry. Harvested cells were resuspended at 4×10^6 /mL in PBS and injected 100 μ L intraperitoneally into female C.B-17 SCID mice. Compounds delineated herein and/or vehicle was orally administered once a day, 5 days per week, starting the day

following the transfer. The transplanted *SCID* mice were weighed weekly and their clinical condition was monitored.

Colon tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Sections (4 μm) collected from ascending, transverse, and descending colon were cut and stained with hematoxylin and eosin. The severity of colitis was determined based on histological examination of the distal colon sections, whereby the extent of colonic inflammation was graded on a scale of 0-3 in each of four criteria: crypt elongation, cell infiltration, depletion of goblet cells, and the number of crypt abscesses.

LP lymphocytes were isolated from freshly obtained colonic specimens. After removal of Peyer's patches, the colon was washed in Ca/Mg-free HBSS, cut into 0.5 cm pieces and incubated twice in HBSS containing EDTA (0.75 mM), DTT (1 mM), and antibiotics (amphotericin 2.5 $\mu\text{g}/\text{mL}$, gentamicin 50 $\mu\text{g}/\text{mL}$ from Sigma) at 37°C for 15 min. Next, the tissue was digested further in RPMI containing 0.5 mg/mL collagenase D, 0.01 mg/mL DNase I (Boehringer Mannheim), and antibiotics at 37°C. LP cells were then layered on a 40-100% Percoll gradient (Pharmacia, Uppsala, Sweden), and lymphocyte-enriched populations were isolated from the cells at the 40-100% interface.

To measure cytokine production, 48-well plates were coated with 10 $\mu\text{g}/\text{mL}$ murine anti-CD3 ϵ antibody (145-2C11) in carbonate buffer (PH 9.6) overnight at 4°C. 5×10^5 LP cells were then cultured in 0.5 ml of complete medium in precoated wells in the presence of 1 $\mu\text{g}/\text{mL}$ soluble anti-CD28 antibody (37.51). Purified antibodies were obtained from Pharmingen. Culture supernatants were removed after 48 h and assayed for cytokine production. Murine IFN γ was measured using an ELISA kit from Endogen (Cambridge, MA), according to the manufacturer's instructions.

Histological analysis showed that oral administration of compounds delineated herein reduced colonic inflammation as compared to vehicle control. The suppressive effect was dose-dependent with a substantial reduction at a dose of 10 mg/kg. The calculated colon-to-body weight ratio was consistent with the histological score, showing attenuation by treatment with the test compound. Furthermore, analysis of cytokines from LP cells in response to anti-CD3 antibody and anti-CD28 antibody demonstrated that LP cells from vehicle control produced an augmented level of IFN γ

and treatment with test substance greatly diminished the production. These results clearly demonstrated the potential of the test substance in treatment of inflammatory bowel disease represented by Crohn's disease.

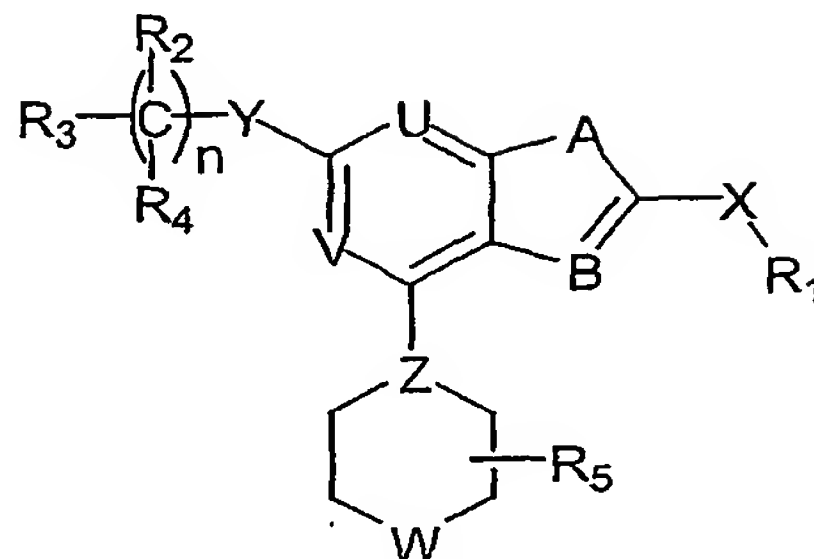
OTHER EMOBDIMENTS

5 All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

10 From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. For example, compounds structurally analogous a compound described in the specification also can be made, screened for
15 their inhibiting IL-12 activities, and used to practice this invention. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein

R_1 is aryl or heteroaryl;

each of R_2 and R_4 , independently, is H, halogen, CN, alkyl, OR^a , or NR^aR^b ;

R_3 is H, halogen, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$, $NR^aC(NR^b)NR^cR^d$, $NR^aC(O)OR^b$, $S(O)NR^aR^b$, $S(O)_2NR^aR^b$, $S(O)R^a$, $S(O)_2R^a$, $C(O)R^a$, $C(O)OR^a$, or $C(O)NR^aR^b$;

R_5 is H or alkyl;

n is 0, 1, 2, 3, 4, 5, or 6;

A is O, S, $S(O)$, $S(O)_2$, or NR^e ;

B is N or CR^f ;

X is O, S, $S(O)$, $S(O)_2$, NR^e , or $C(O)$;

Y is a covalent bond, $C(O)$, $C=NR^a$, O, S, $S(O)$, $S(O)_2$, or NR^e ;

Z is N or CH;

each of U and V, independently, is N or CR; and

W is O, S, or NR^e ;

in which each of R^a , R^b , R^c , and R^d , independently, is H, alkyl, aryl, heteroaryl, cyclyl, or heterocyclyl; R^e is H, alkyl, aryl, acyl, or sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxyl, amino, ester, amide, CN, or halogen; and

provided that if each of U and V is N, Y is a covalent bond, n is 0, then R_3 is

H, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$,

$\text{NR}^a\text{C}(\text{NR}^b)\text{NR}^c\text{R}^d$, $\text{NR}^a\text{C}(\text{O})\text{OR}^b$, $\text{S}(\text{O})\text{NR}^a\text{R}^b$, $\text{S}(\text{O})_2\text{NR}^a\text{R}^b$, $\text{S}(\text{O})\text{R}^a$, $\text{S}(\text{O})_2\text{R}^a$, $\text{C}(\text{O})\text{R}^a$, $\text{C}(\text{O})\text{OR}^a$, or $\text{C}(\text{O})\text{NR}^a\text{R}^b$.

2. The compound of claim 1, wherein A is NR^e , and B is N.

3. The compound of claim 1, wherein Z is N.

4. The compound of claim 3, wherein W is O.

5. The compound of claim 1, wherein X is NR^e .

6. The compound of claim 1, wherein each of U and V is N.

7. The compound of claim 6, wherein A is NR^e and B is N.

8. The compound of claim 6, wherein Z is N.

9. The compound of claim 8, wherein W is O.

10. The compound of claim 6, wherein X is NR^e .

11. The compound of claim 10, wherein A is NR^e and B is N.

12. The compound of claim 11, wherein Z is N.

13. The compound of claim 12, wherein W is O.

14. The compound of claim 12, wherein R_3 is halogen, CN, alkyl, aryl, heteroaryl, OR^a , $\text{OC}(\text{O})\text{R}^a$, NR^aNR^b , $\text{NR}^a\text{C}(\text{O})\text{R}^b$, $\text{C}(\text{O})\text{OR}^a$, or $\text{C}(\text{O})\text{NR}^a\text{R}^b$.

15. The compound of claim 14, wherein R_3 is aryl, heteroaryl, aryloxy, or heteroaryloxy.

16. The compound of claim 15, wherein R_3 is heteroaryl.

17. The compound of claim 15, wherein R_3 is pyridinyl, triazolyl,
5 tetrazolyl, pyrimidinyl, thiazolyl, indolyl, or indolizinyl.

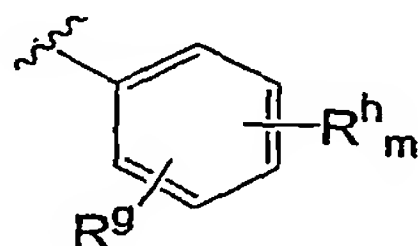
18. The compound of claim 15, wherein the compound is a *N*-oxide.

19. The compound of claim 13, wherein R_1 is aryl.

20. The compound of claim 19, wherein Y is NR^e .

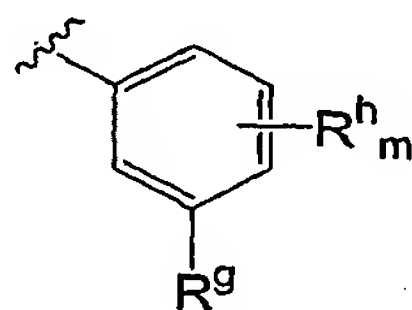
21. The compound of claim 19, wherein Y is O.

22. The compound of claim 19, wherein R_1 is

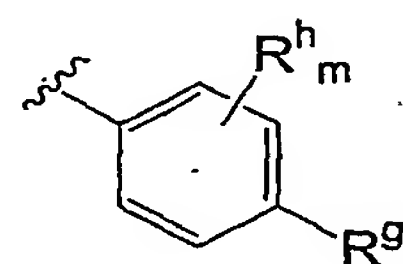


in which R^e is H, halogen, CN, alkyl, or alkoxy; R^h is halogen, CN, hydroxyl, amino, alkyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, acyl, alkoxycarbonyl, alkylcarbonoxyl, mono- and dialkylaminocarbonyl, amidinyl, ureayl, guanadinyl,
20 sulfonyl, or sufonamidyl; and m is 0, 1, 2, 3, or 4.

23. The compound of claim 22, wherein R_1 is

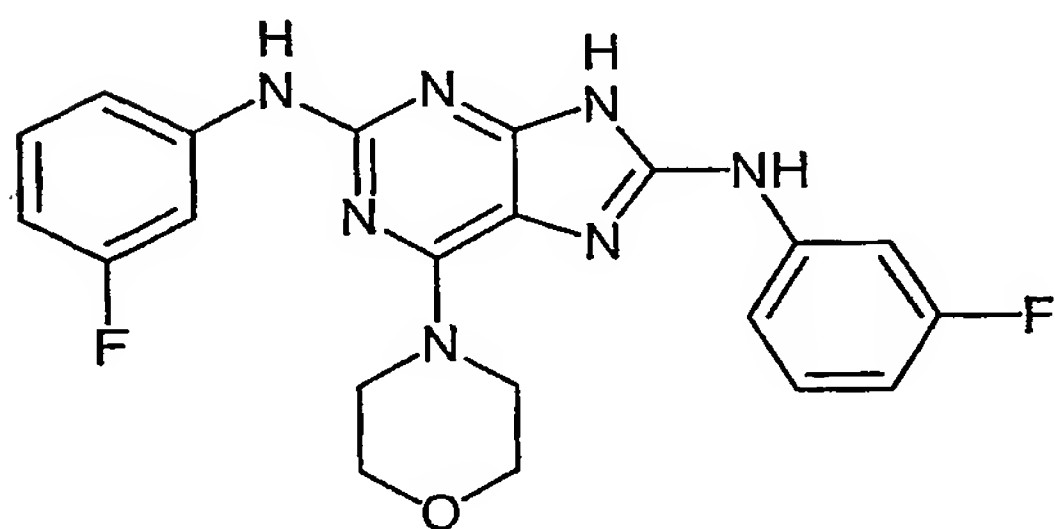
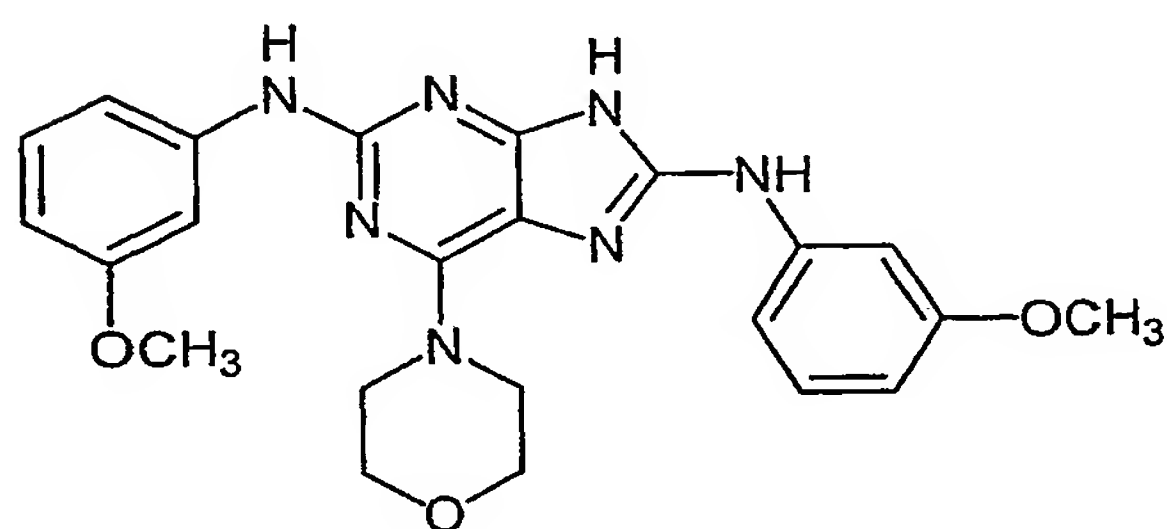
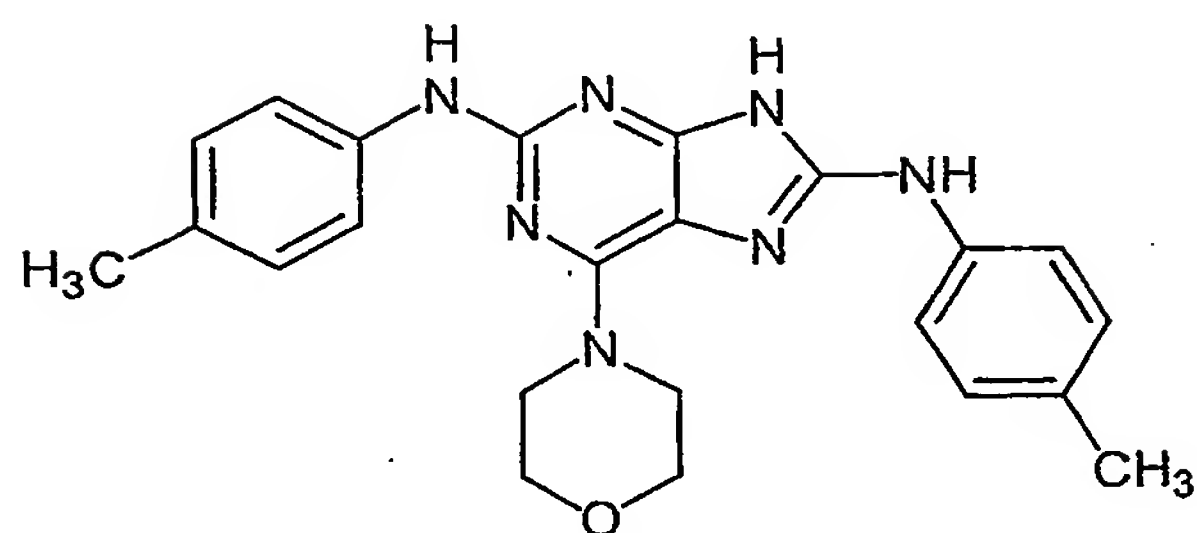


or

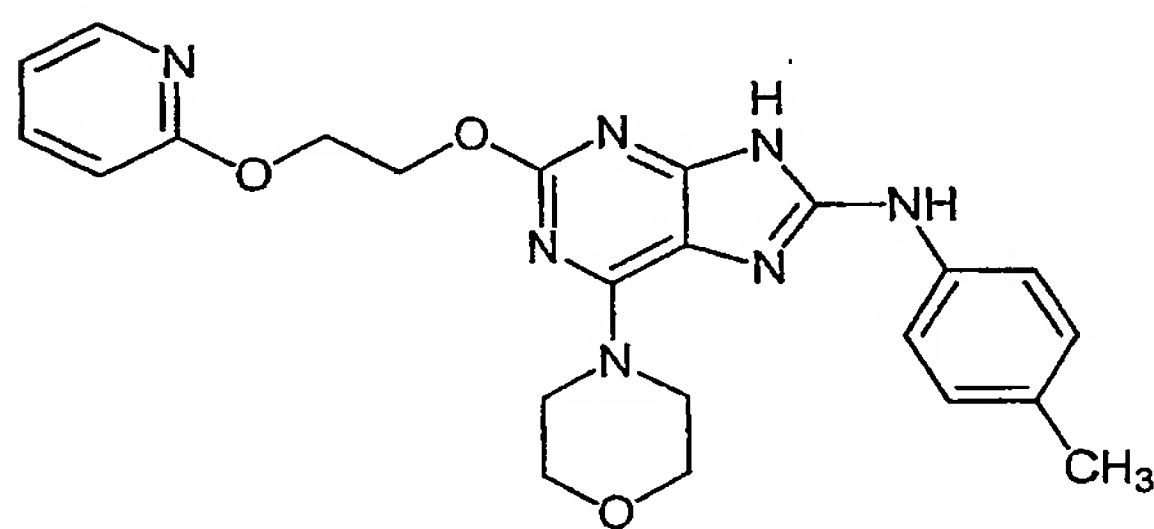


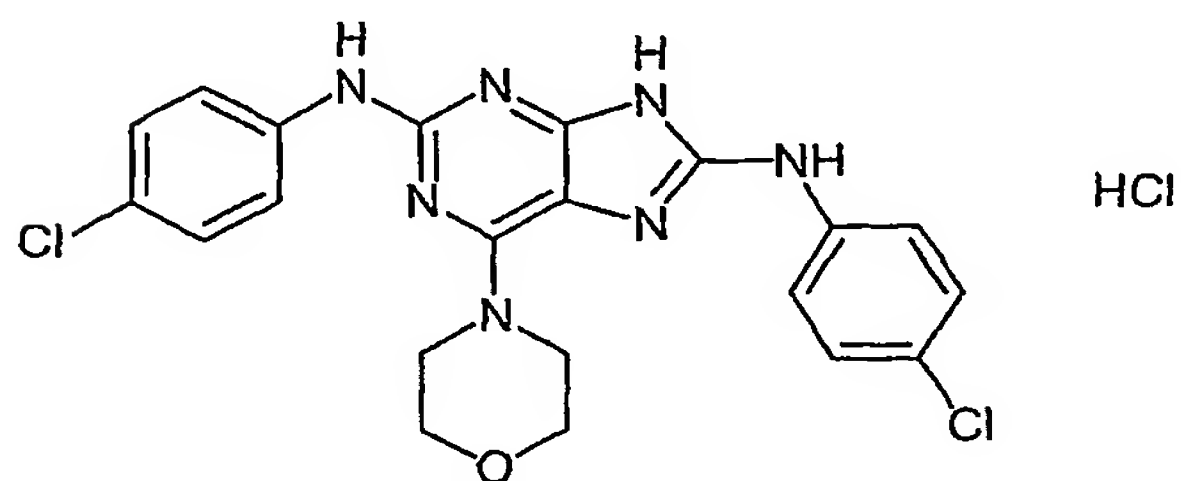
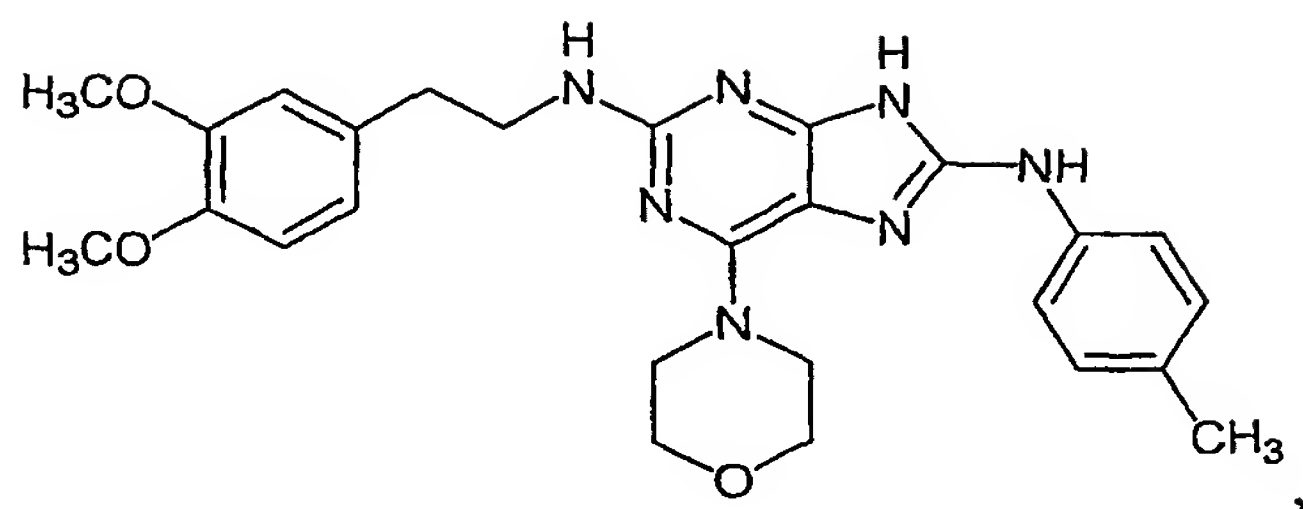
24. The compound of claim 22, wherein R^e is H, F, Cl, Br, I, CN, Me, Et, Pr, *i*-Pr, OMe, or OEt.

25. The compound of claim 1, wherein the compound is

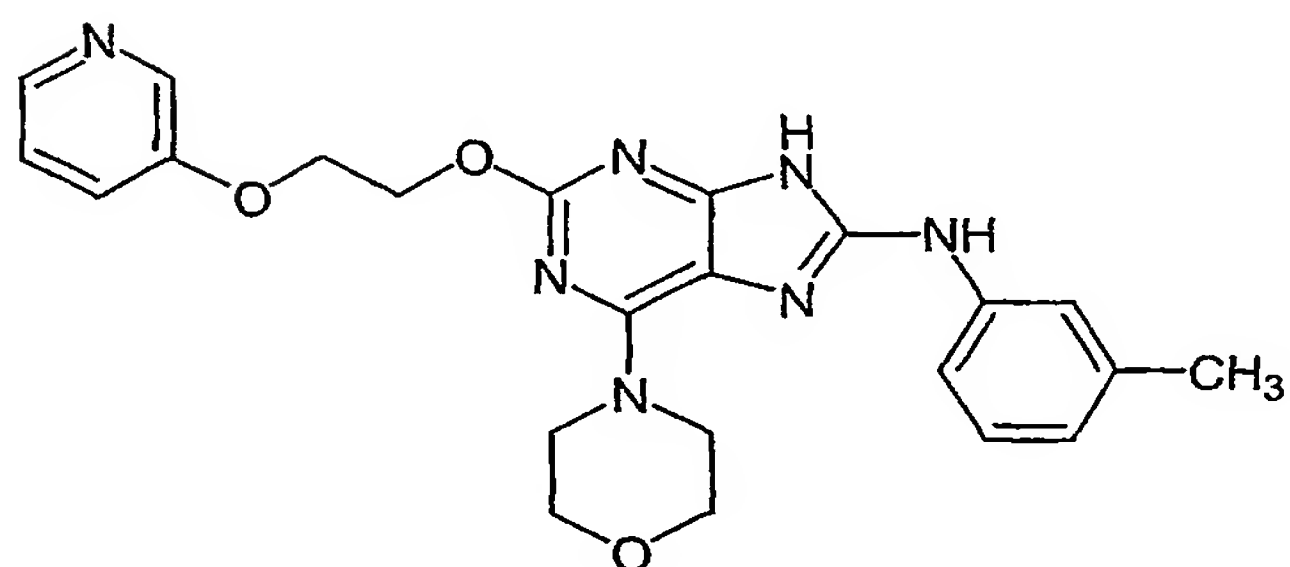
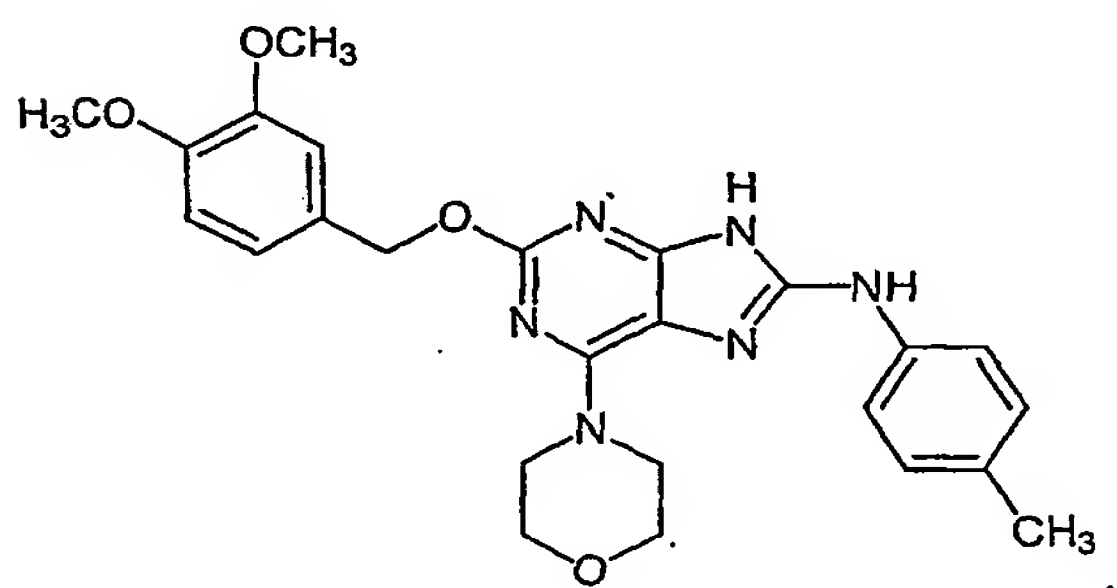


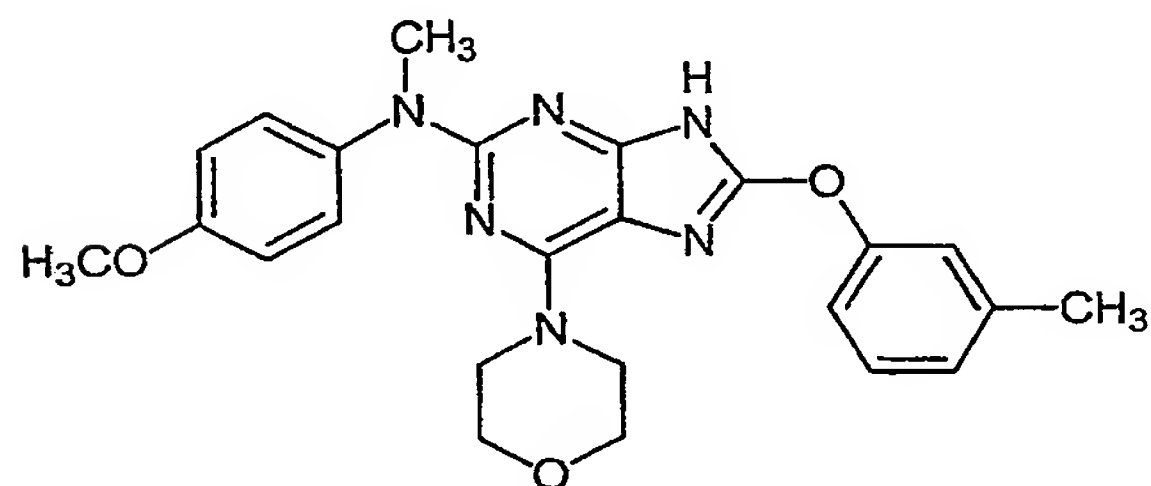
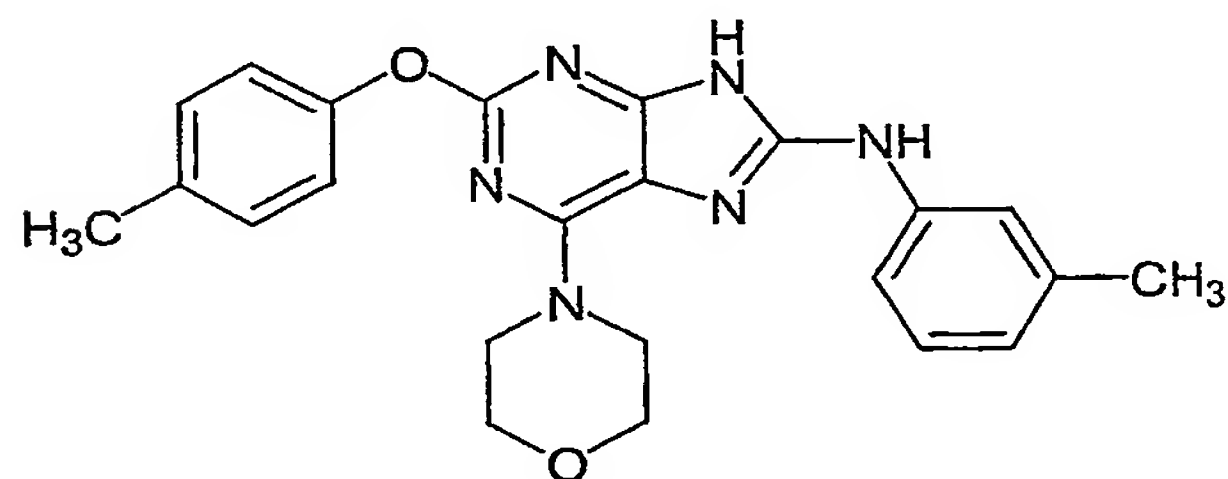
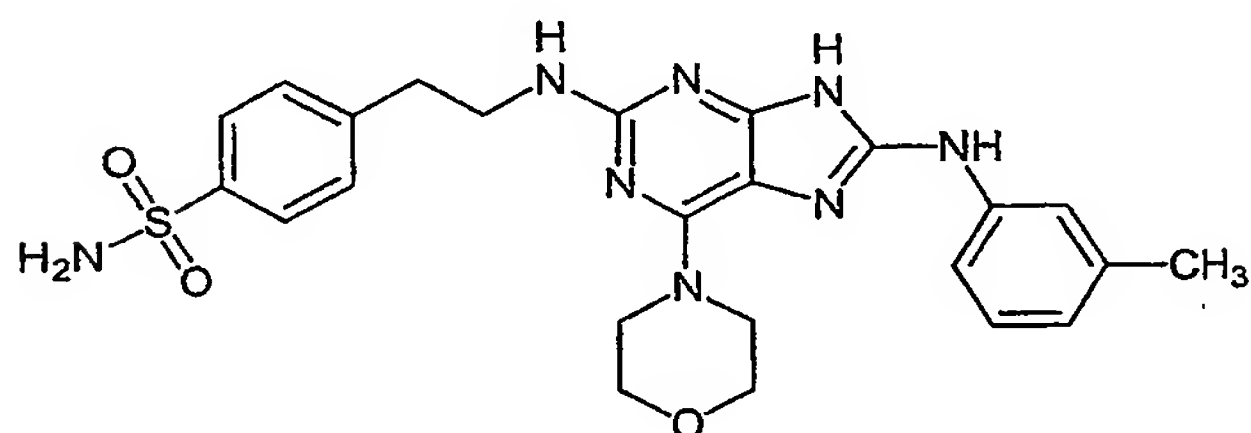
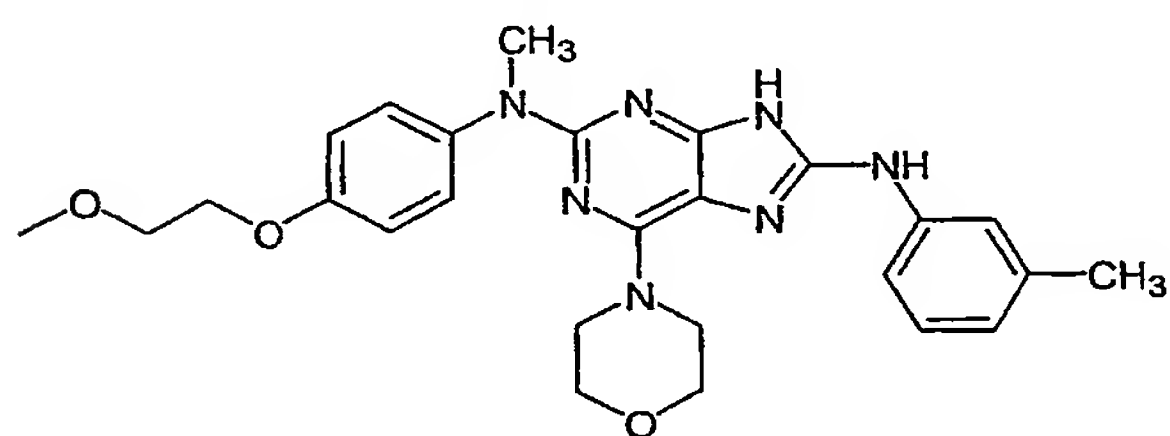
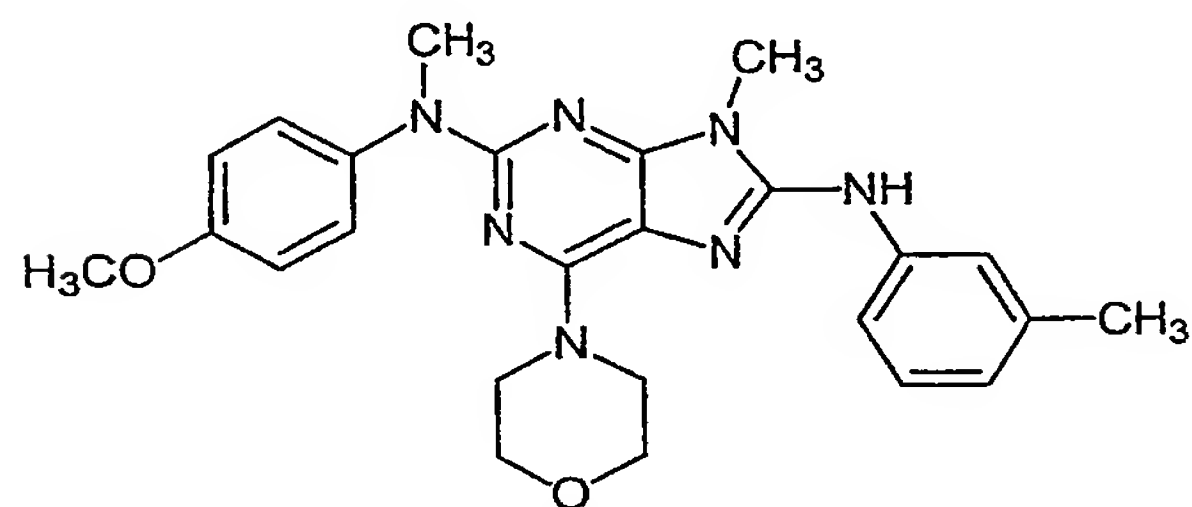
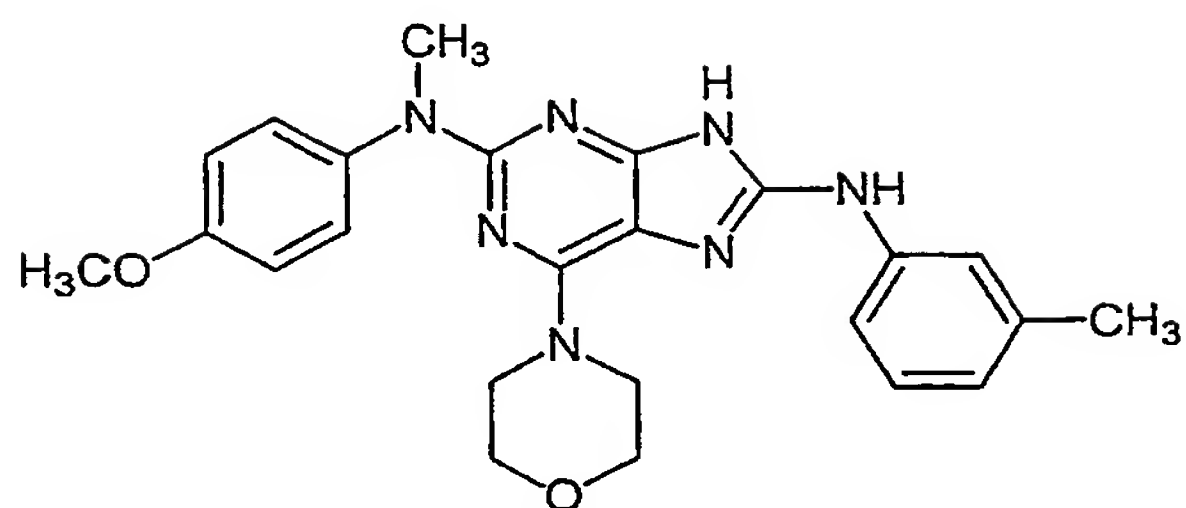
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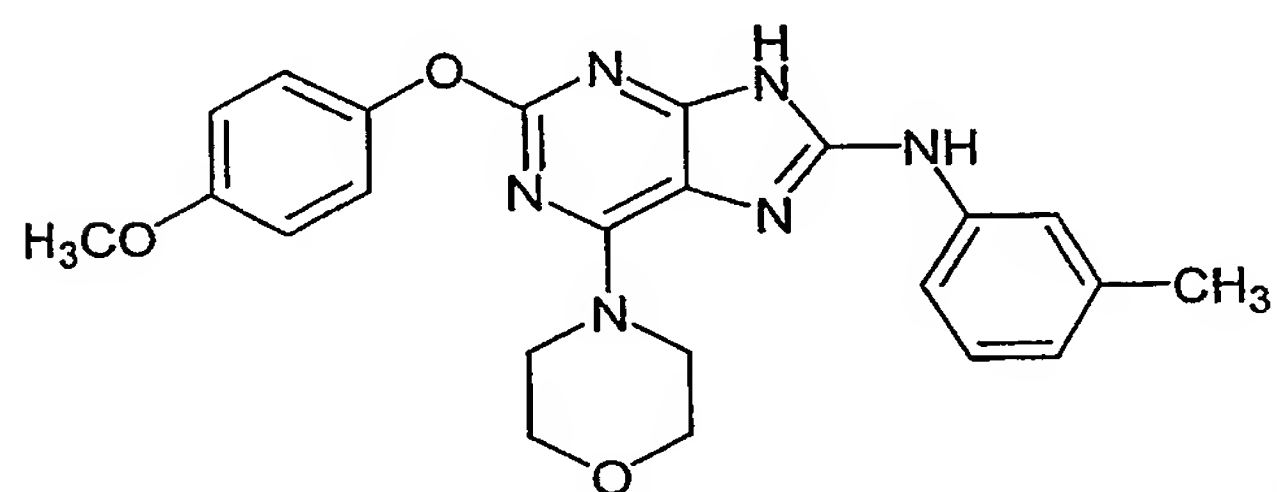
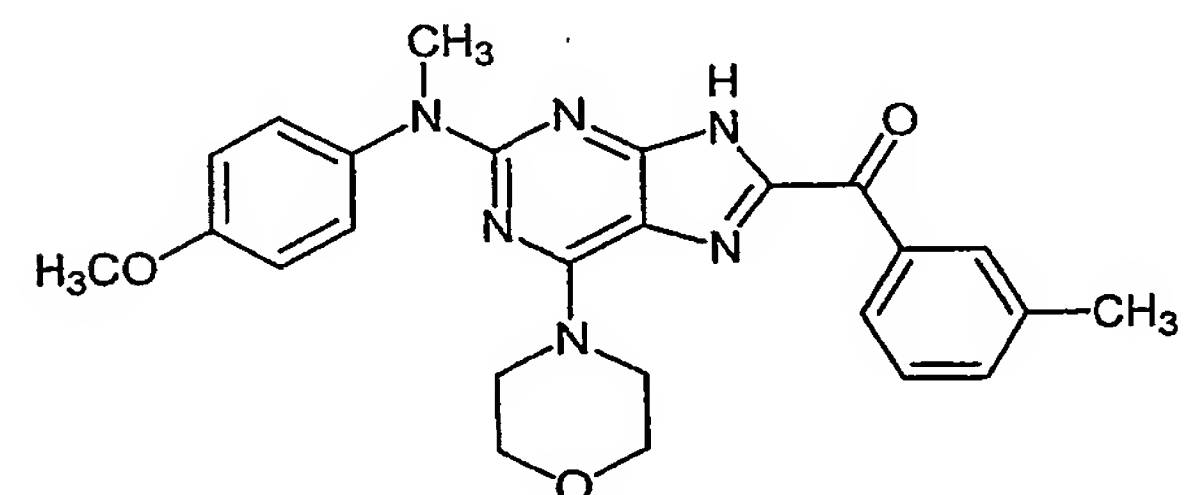
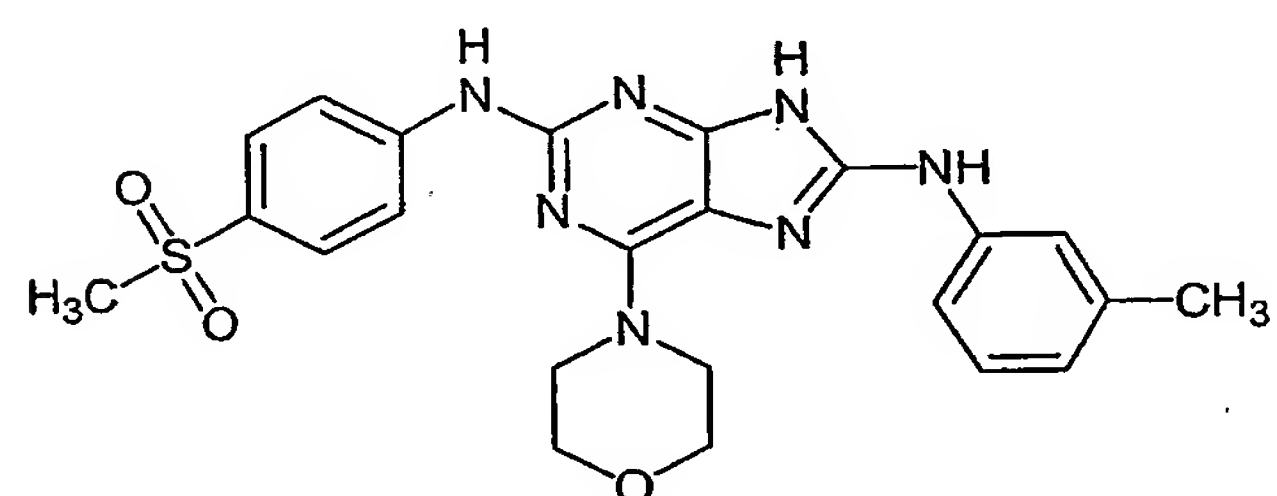
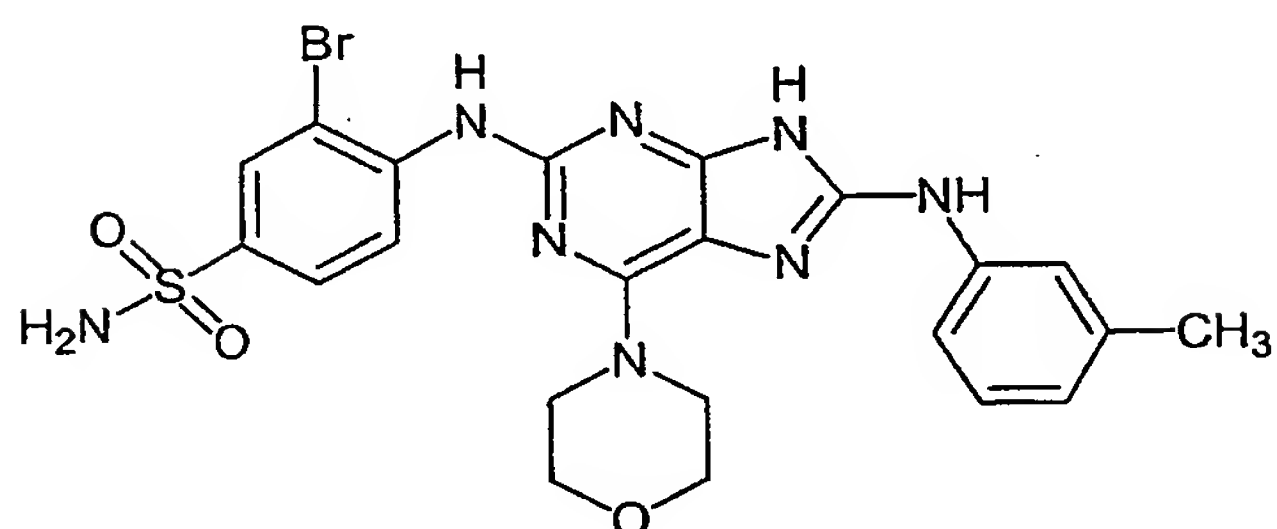
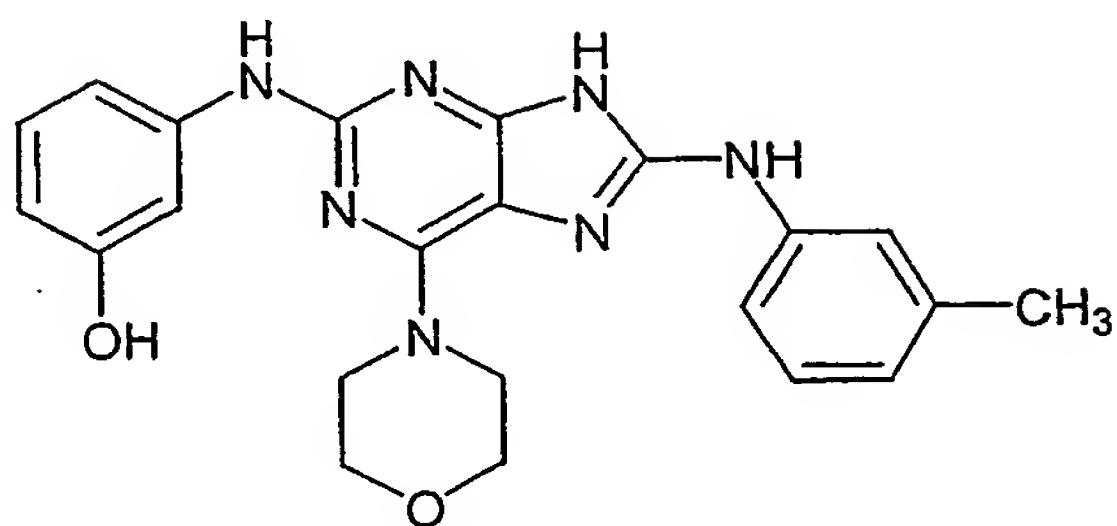




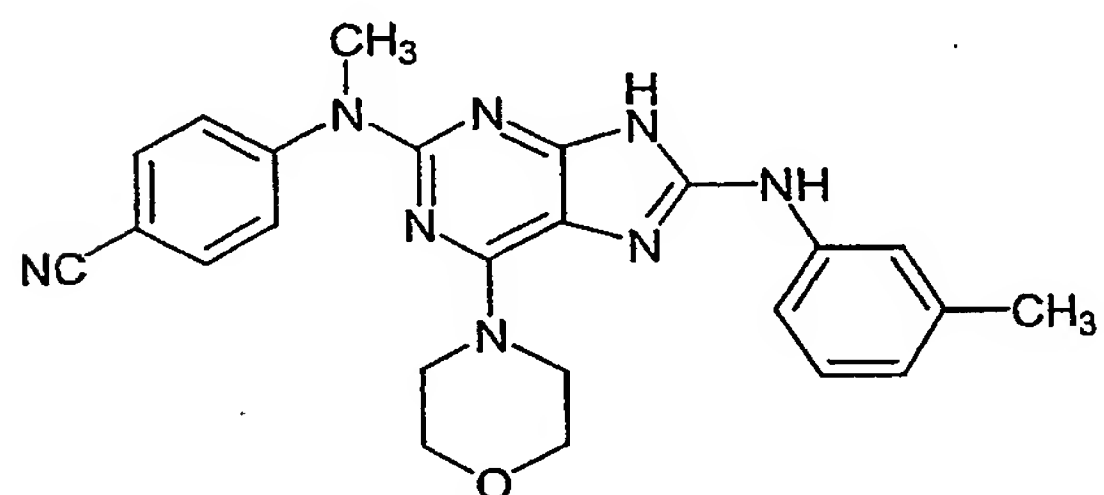
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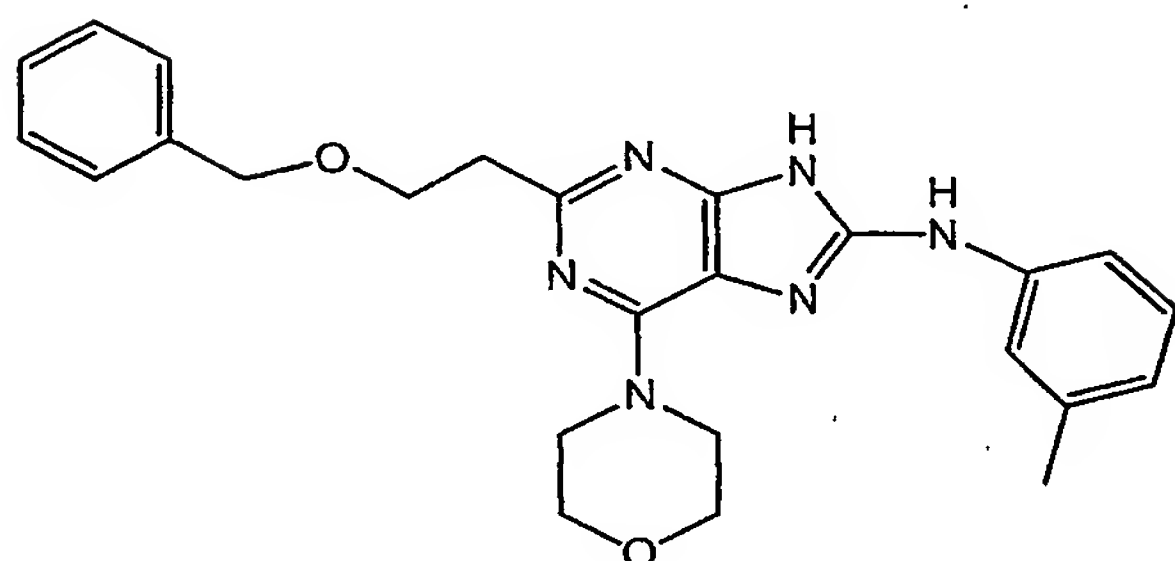
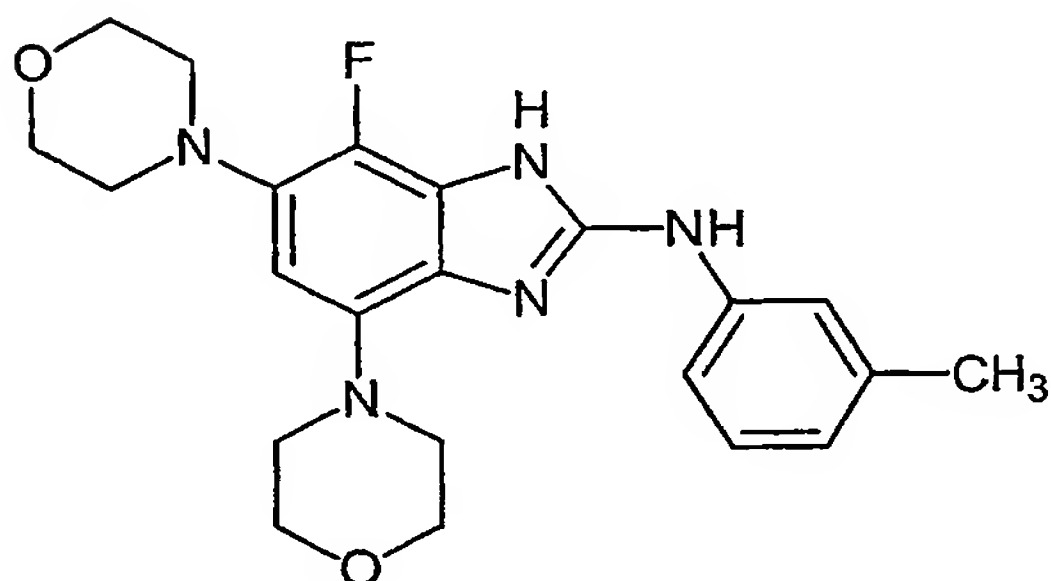
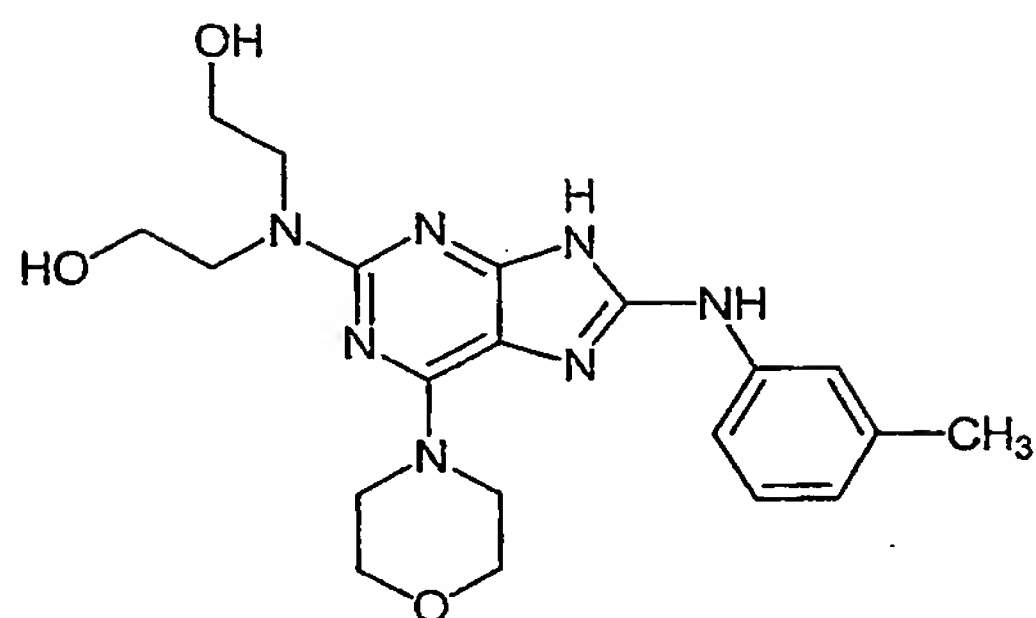




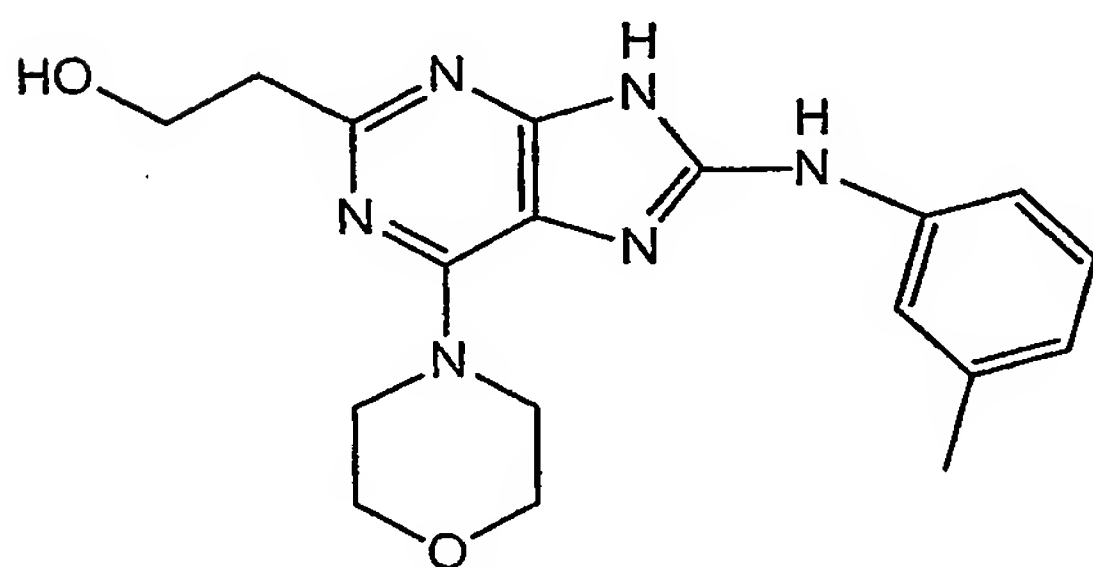


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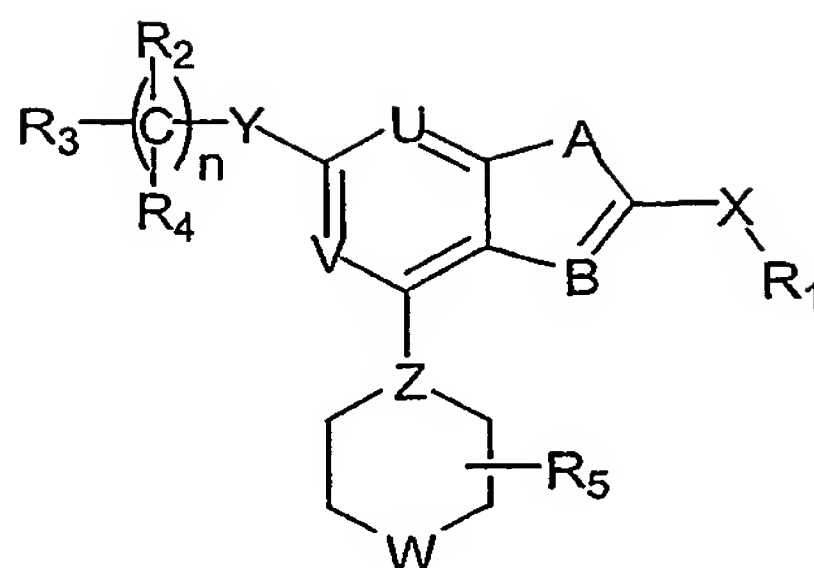


, or



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26. A method for treating an interleukin-12 overproduction-related disorder, comprising administering to a subject in need thereof an effective amount of the compound of formula (I):



wherein

R_1 is aryl or heteroaryl;

each of R_2 and R_4 , independently, is H, halogen, CN, alkyl, OR^a , or NR^aR^b ;

5 R_3 is H, halogen, CN, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, OR^a , $OC(O)R^a$, $OC(O)NR^aR^b$, NR^aR^b , $NR^aC(O)R^b$, $NR^aS(O)R^b$, $NR^aS(O)_2R^b$, $NR^aC(O)NR^bR^c$, $NR^aC(S)NR^bR^c$, $NR^aC(NR^b)NR^cR^d$, $NR^aC(O)OR^b$, $S(O)NR^aR^b$, $S(O)_2NR^aR^b$, $S(O)R^a$, $S(O)_2R^a$, $C(O)R^a$, $C(O)OR^a$, or $C(O)NR^aR^b$;

R_5 is H or alkyl;

10 n is 0, 1, 2, 3, 4, 5, or 6;

A is O, S, $S(O)$, $S(O)_2$, or NR^e ;

B is N or CR^f ;

X is O, S, $S(O)$, $S(O)_2$, NR^e , or $C(O)$;

Y is a covalent bond, $C(O)$, $C=NR^a$, O, S, $S(O)$, $S(O)_2$, or NR^e ;

15 Z is N or CH;

each of U and V , independently, is N or CR ; and

W is O, S, or NR^e ;

in which each of R^a , R^b , R^c , and R^d , independently, is H, alkyl, aryl, heteroaryl, cyclyl, or heterocyclyl; R^e is H, alkyl, aryl, acyl, or sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxy, amino, ester, amide, CN, or halogen.

20

27. The method of claim 26, wherein A is NR^e , and B is N.

28. The method of claim 26, wherein Z is N.

25

29. The method of claim 28, wherein W is O.

30. The method of claim 26, wherein X is NR^e .

31. The method of claim 26, wherein each of U and V is N.

5 32. The method of claim 26, wherein the disorder is rheumatoid arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or insulin-dependent diabetes mellitus.

33. The method of claim 32, wherein A is NR^e , and B is N.

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34. The method of claim 32, wherein Z is N.

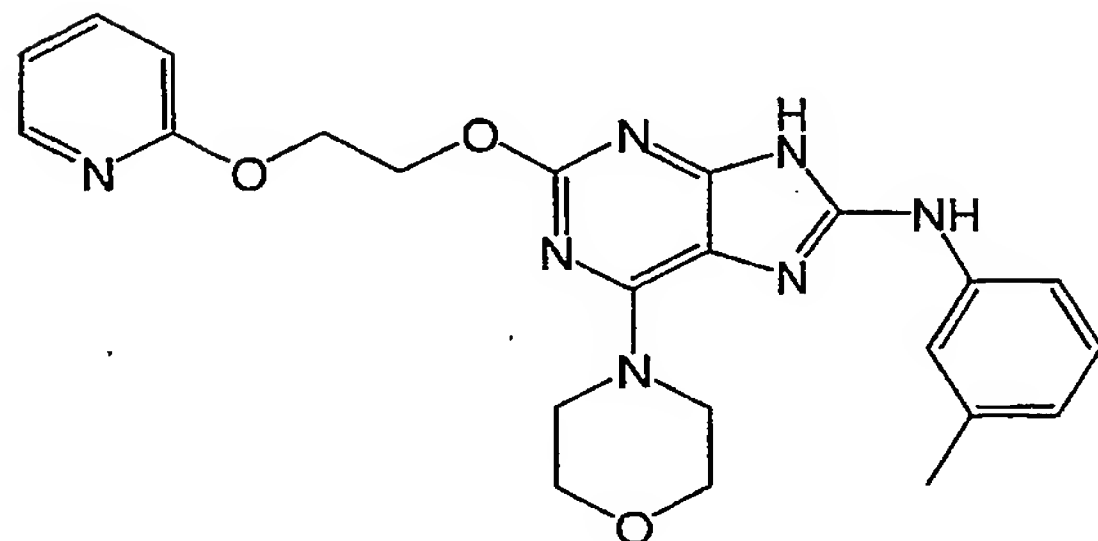
35. The method of claim 34, wherein W is O.

15

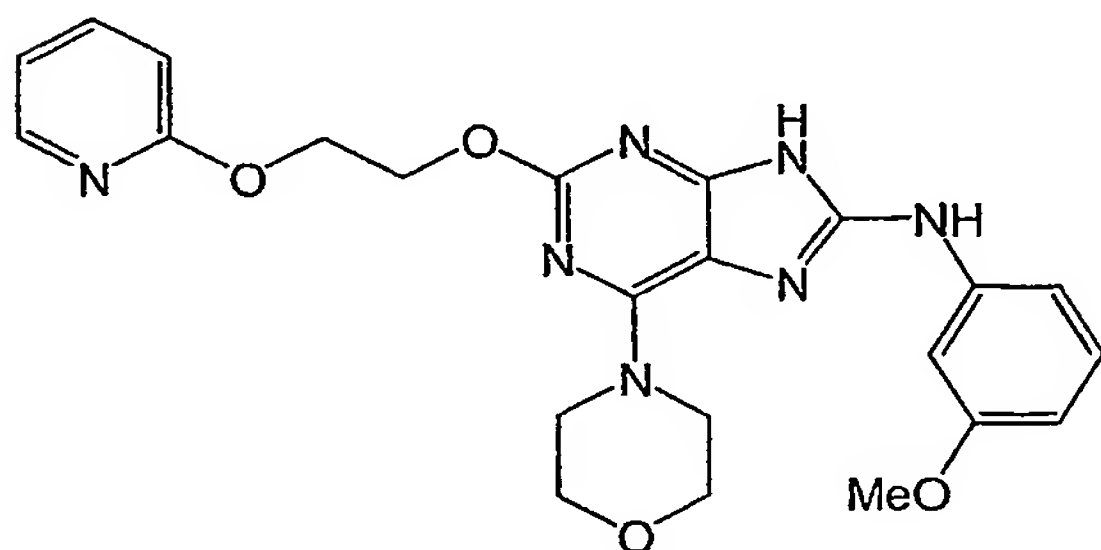
36. The method of claim 32, wherein X is NR^e .

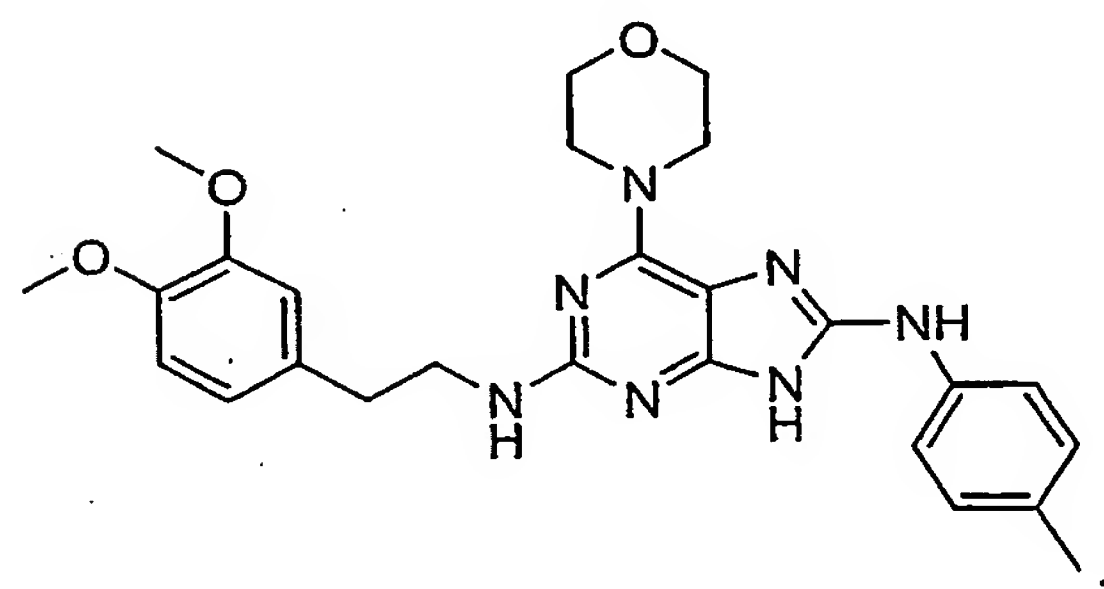
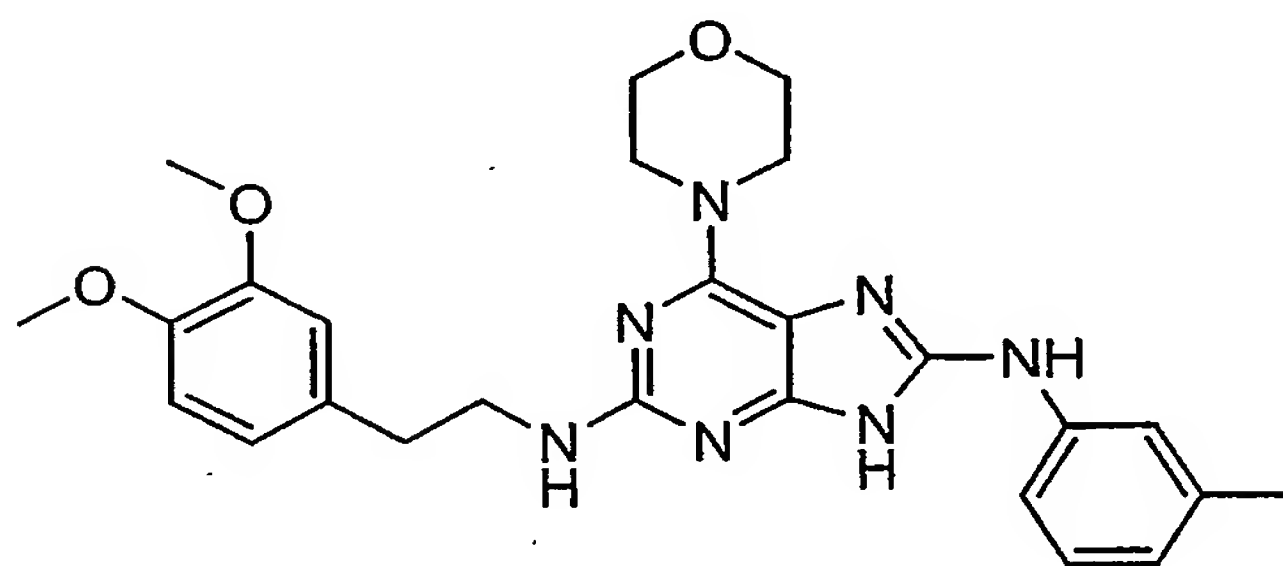
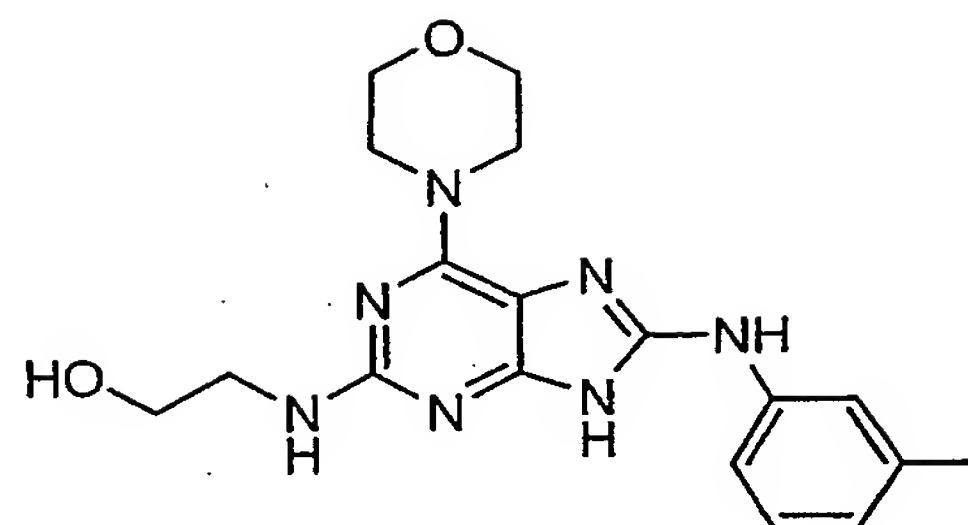
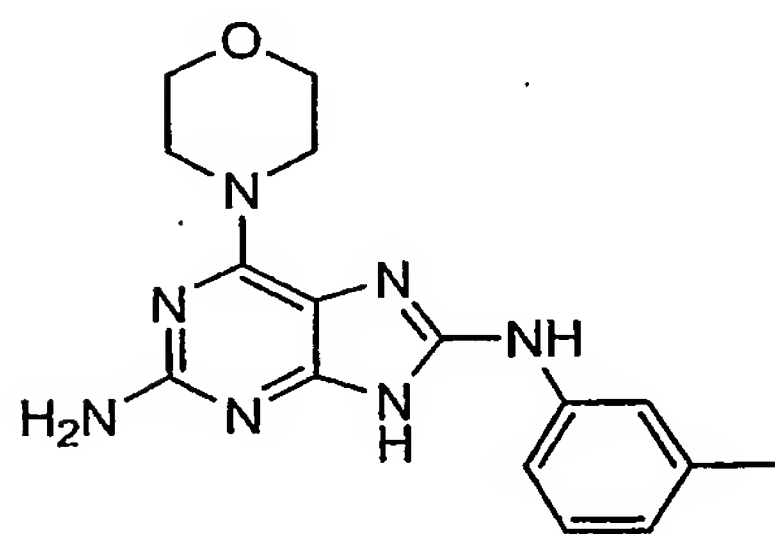
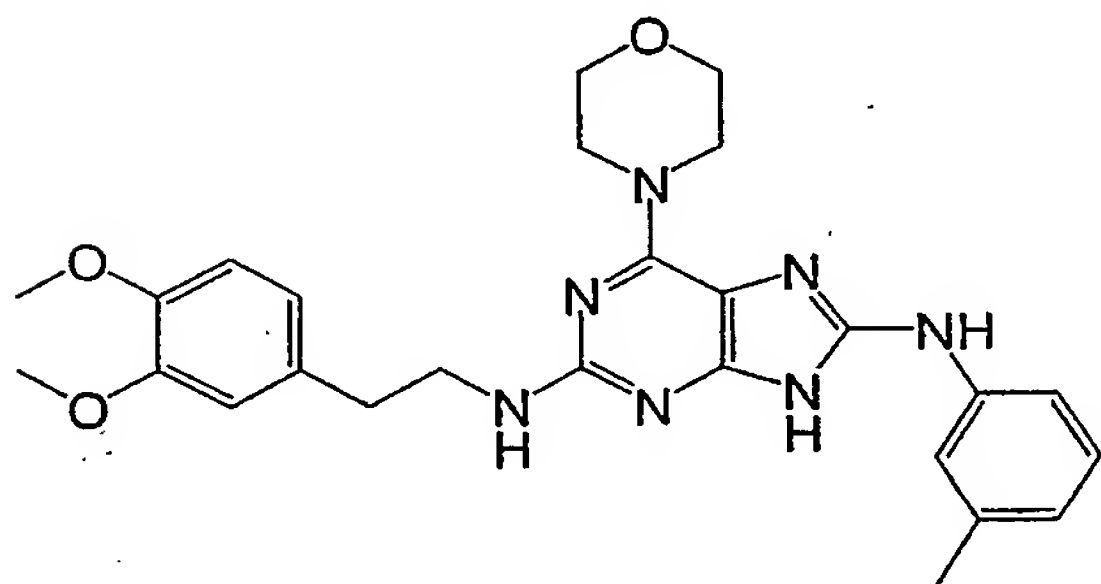
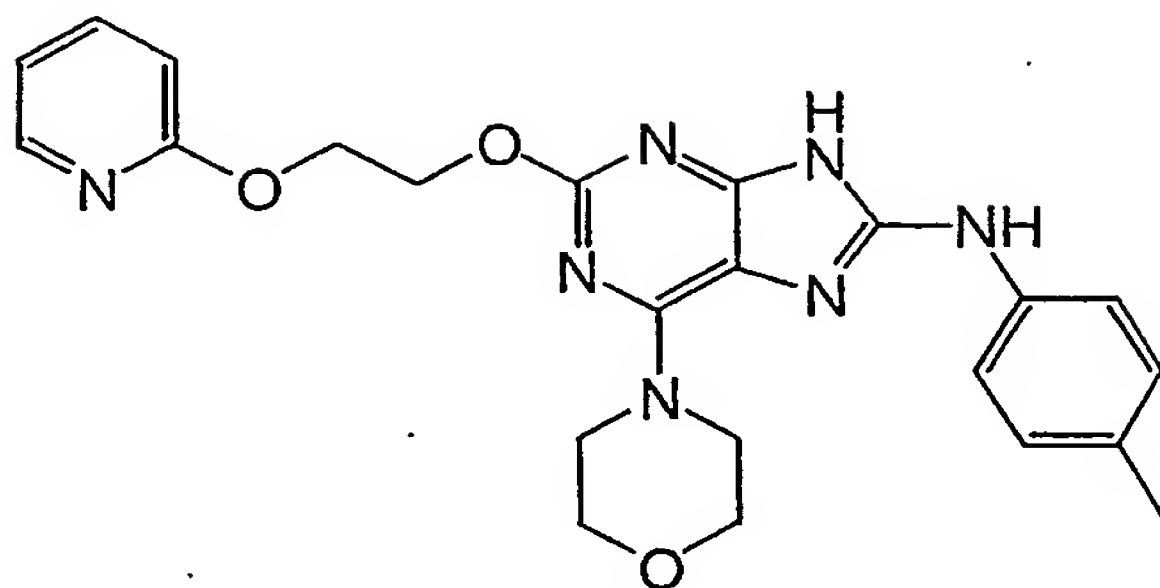
37. The method of claim 32, wherein each of U and V is N.

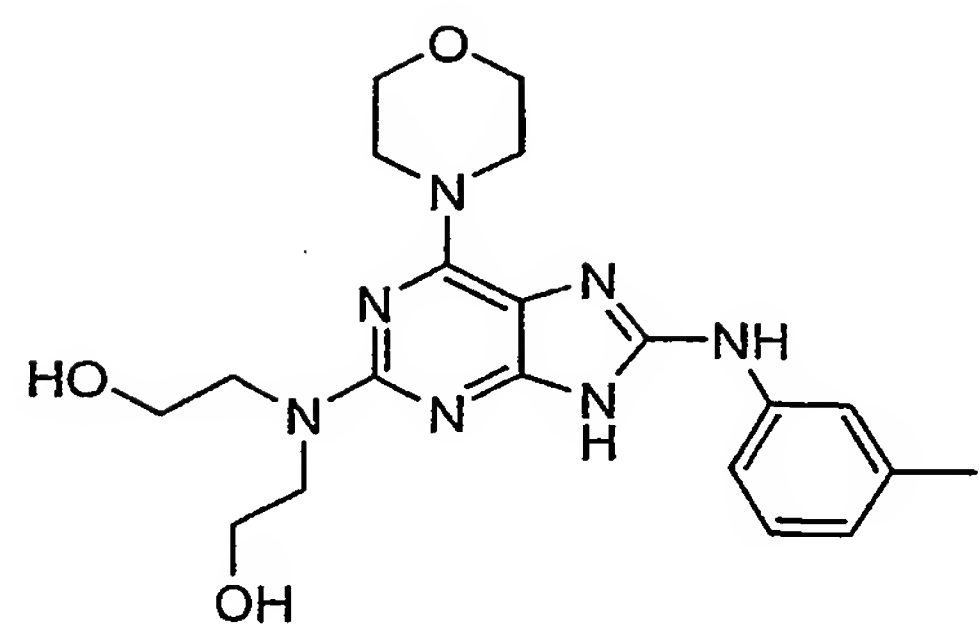
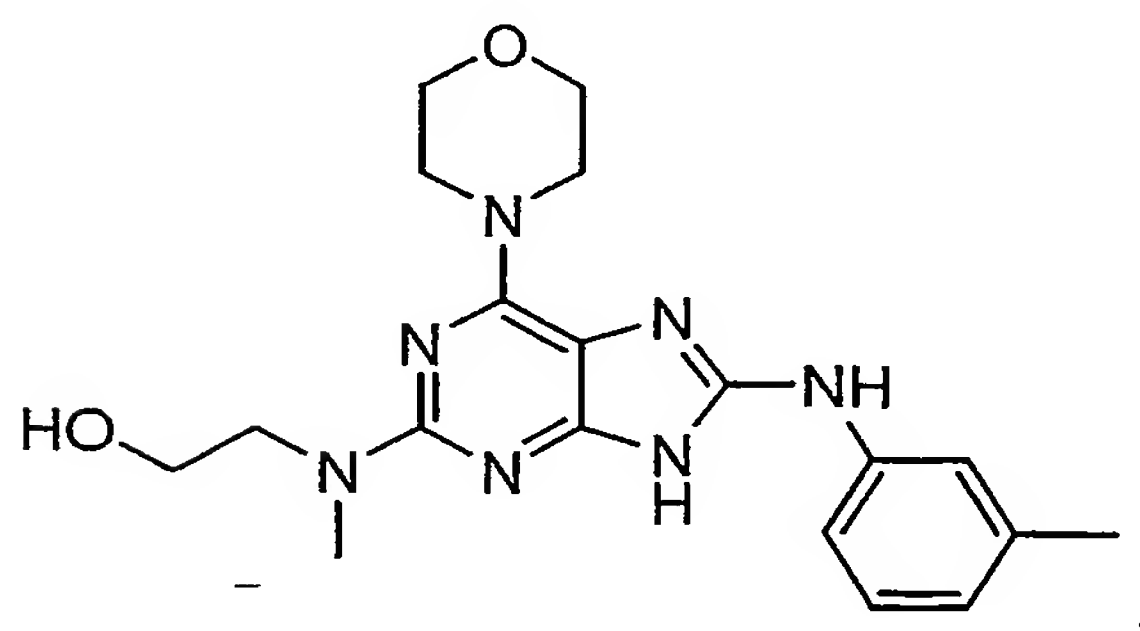
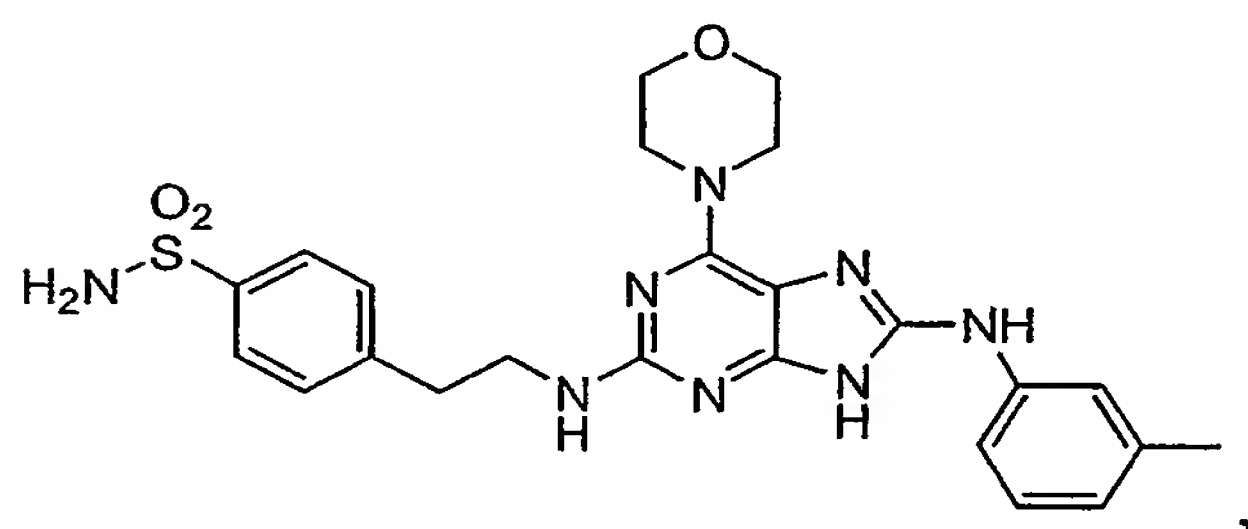
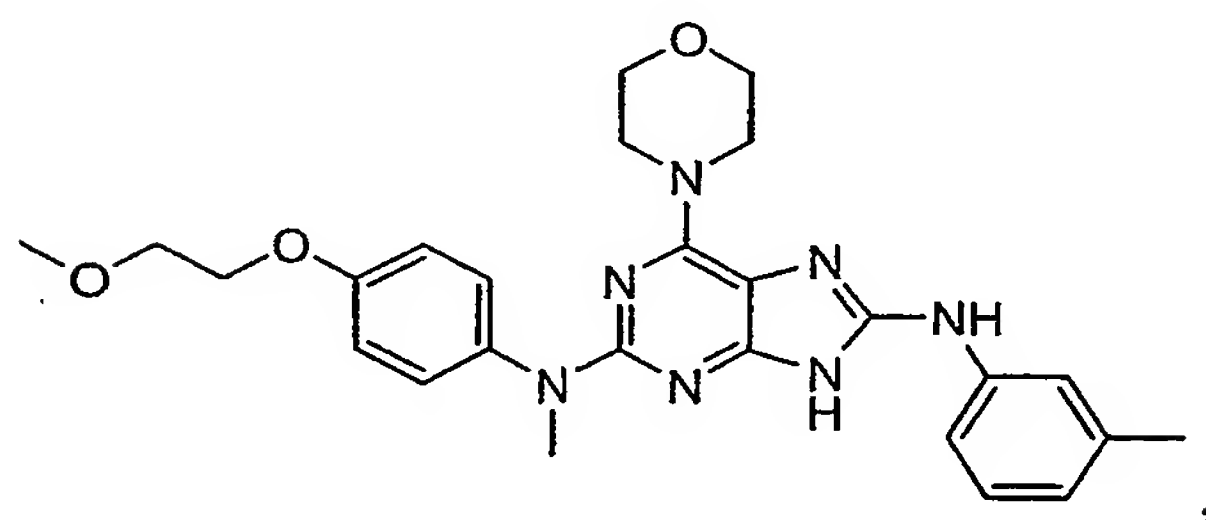
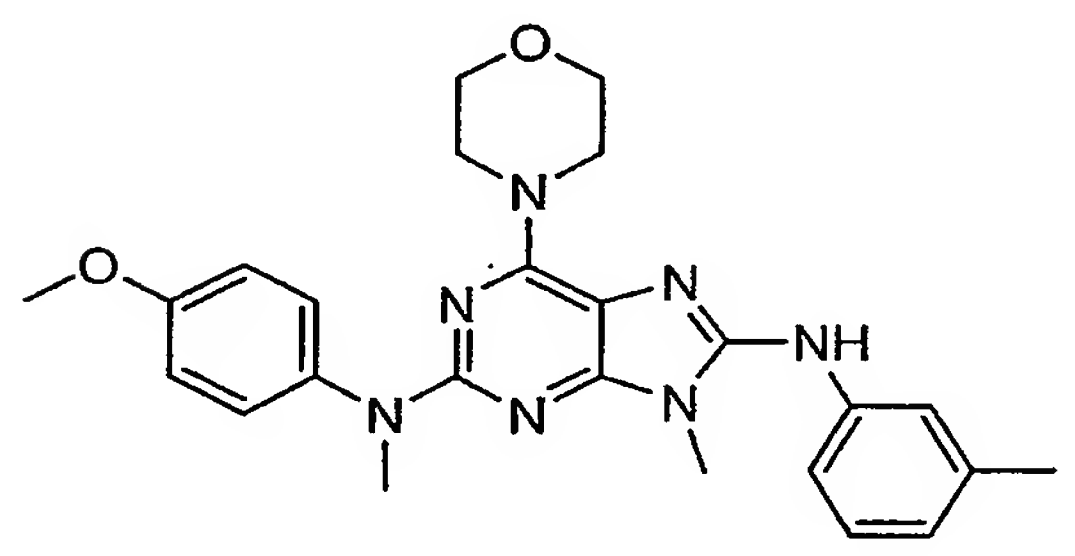
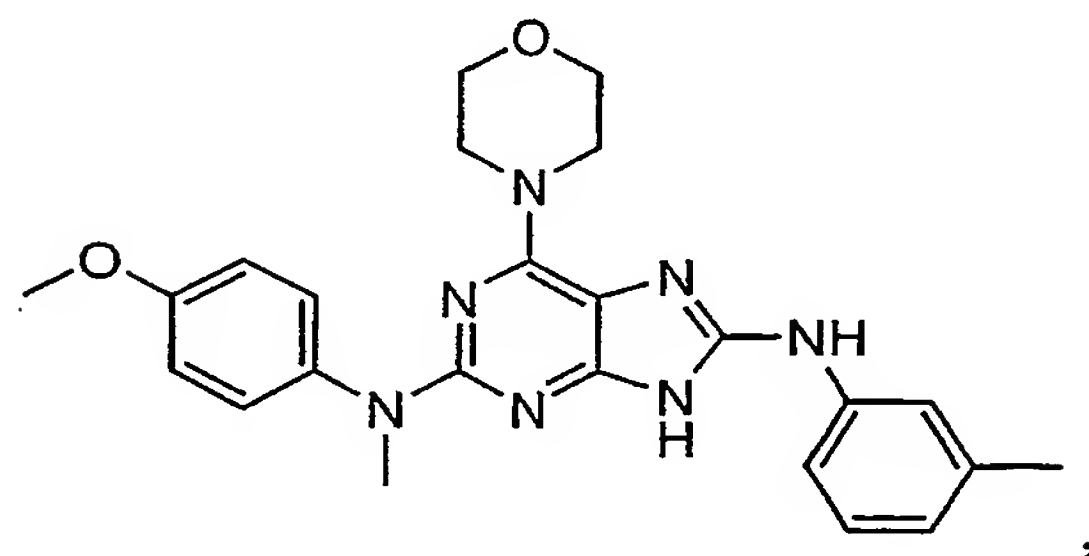
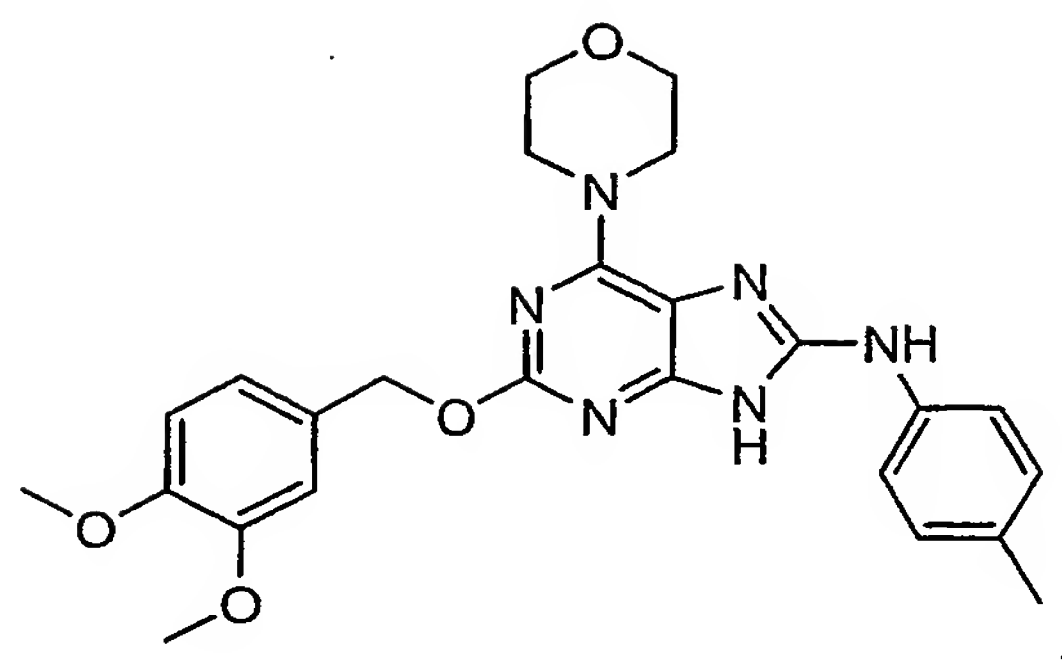
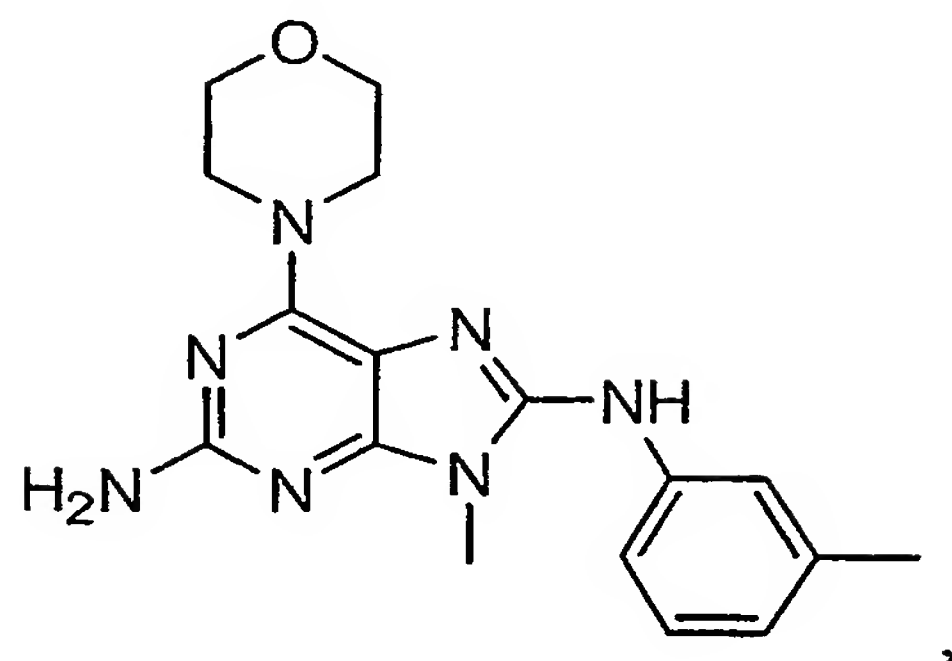
38. The method of claim 26, wherein the compound is

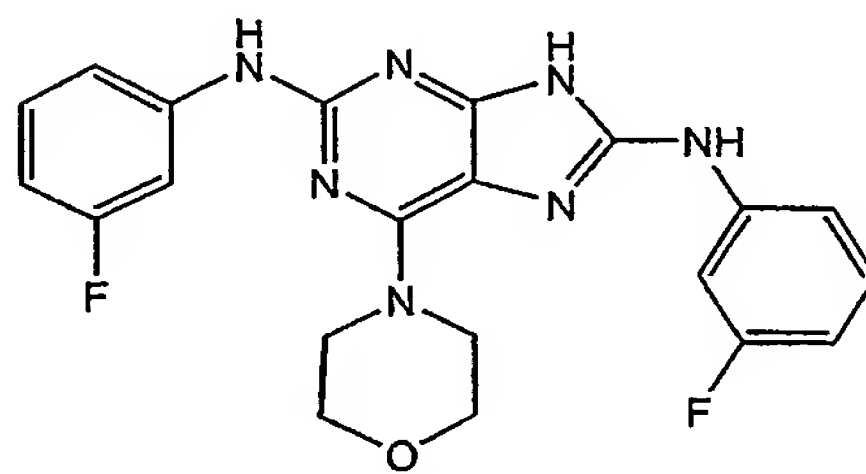
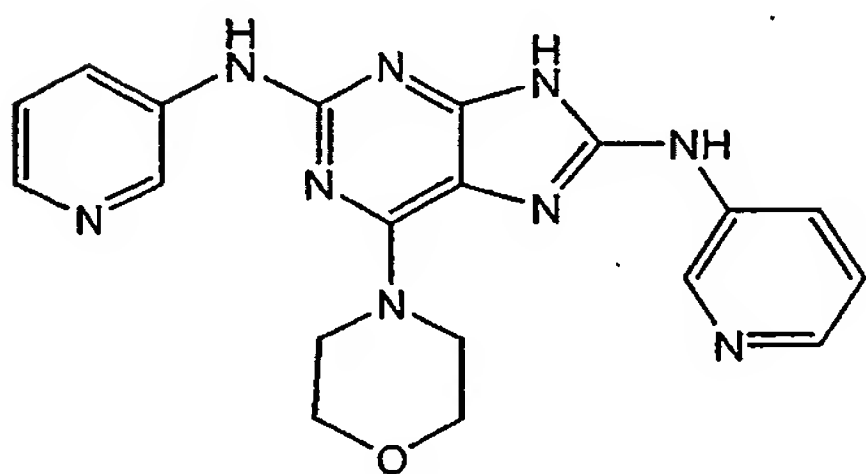
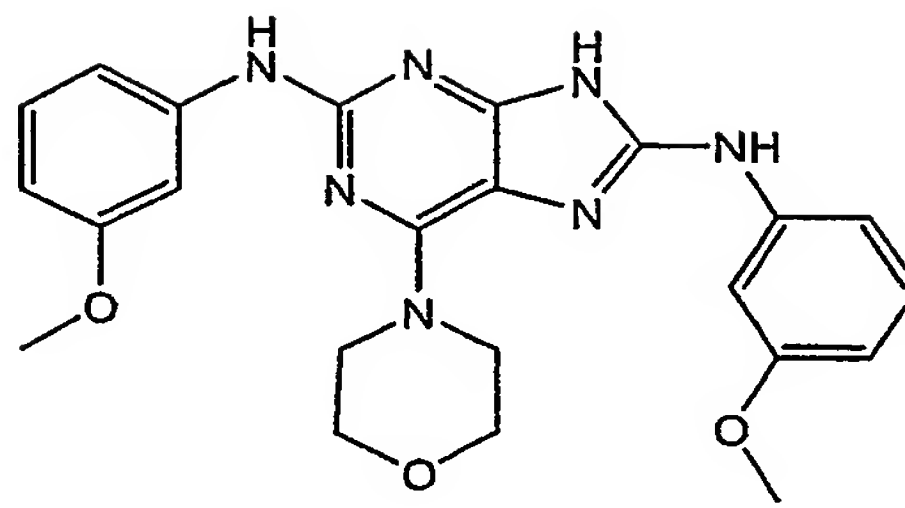
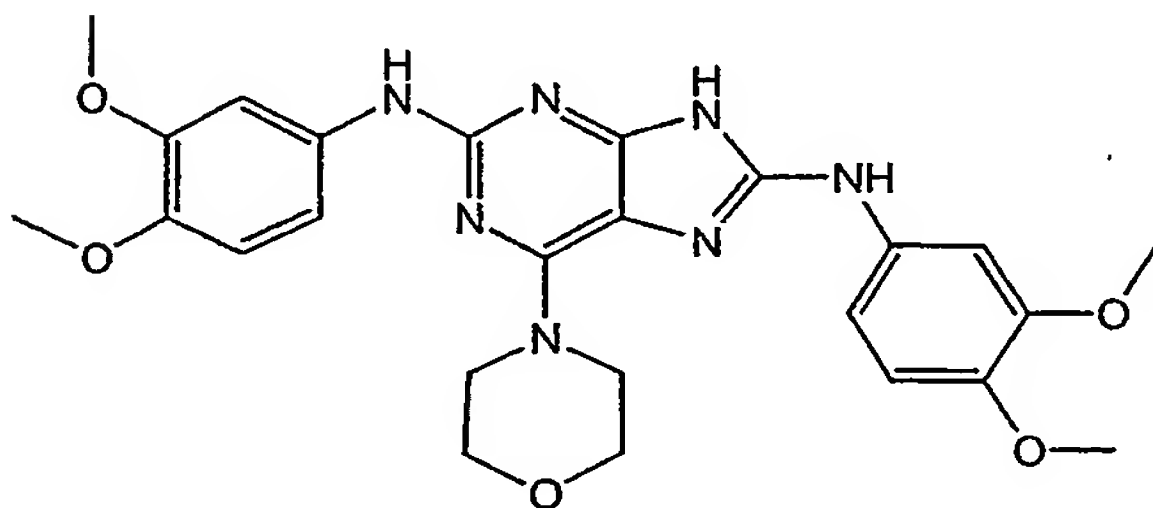
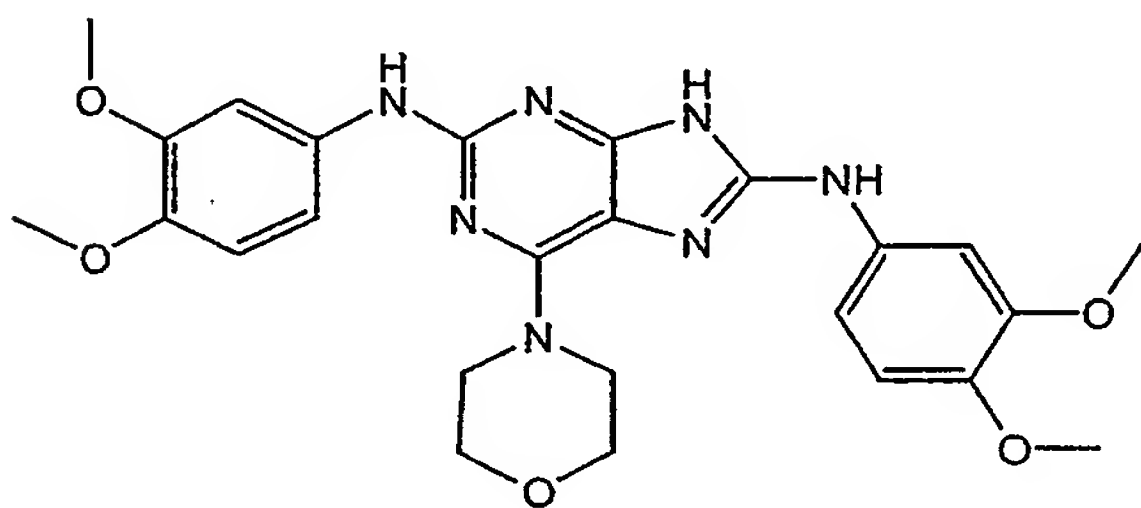
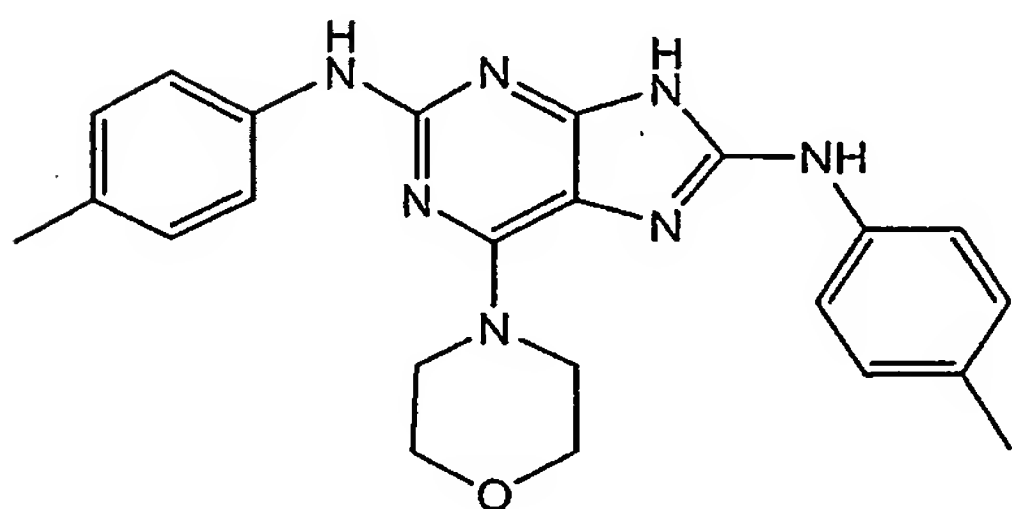
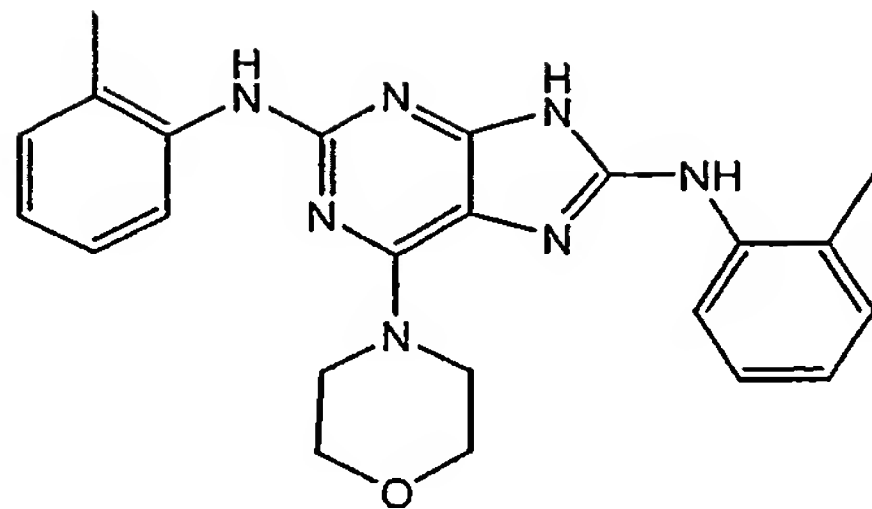
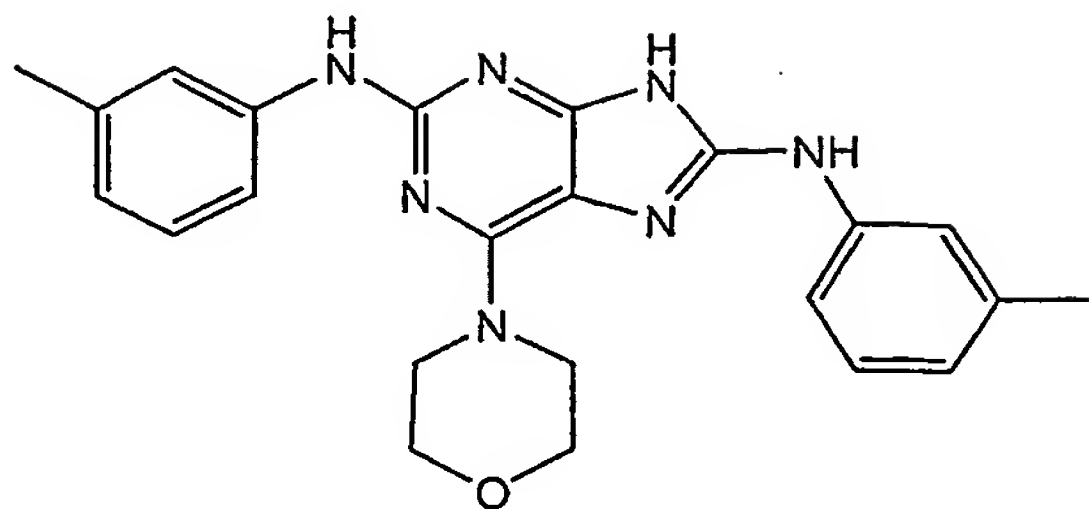


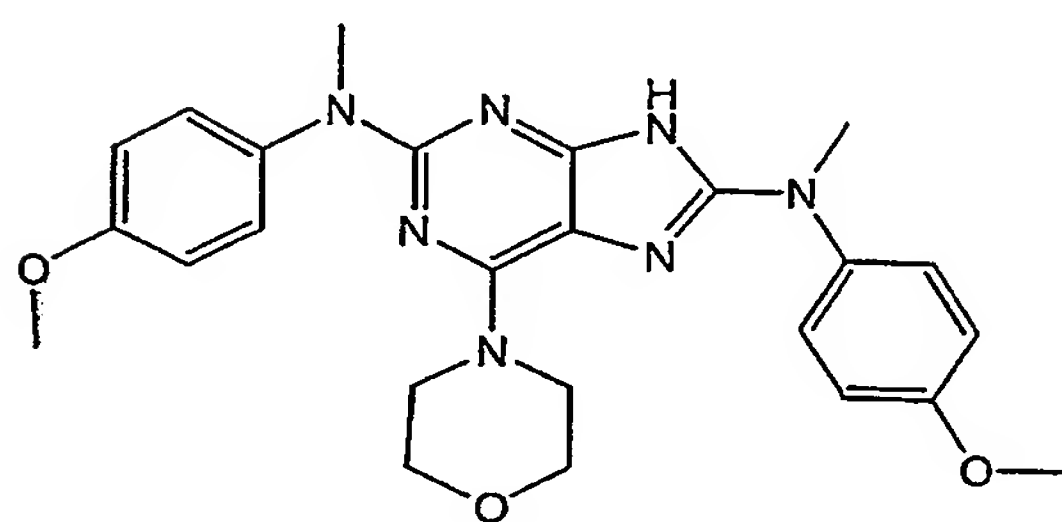
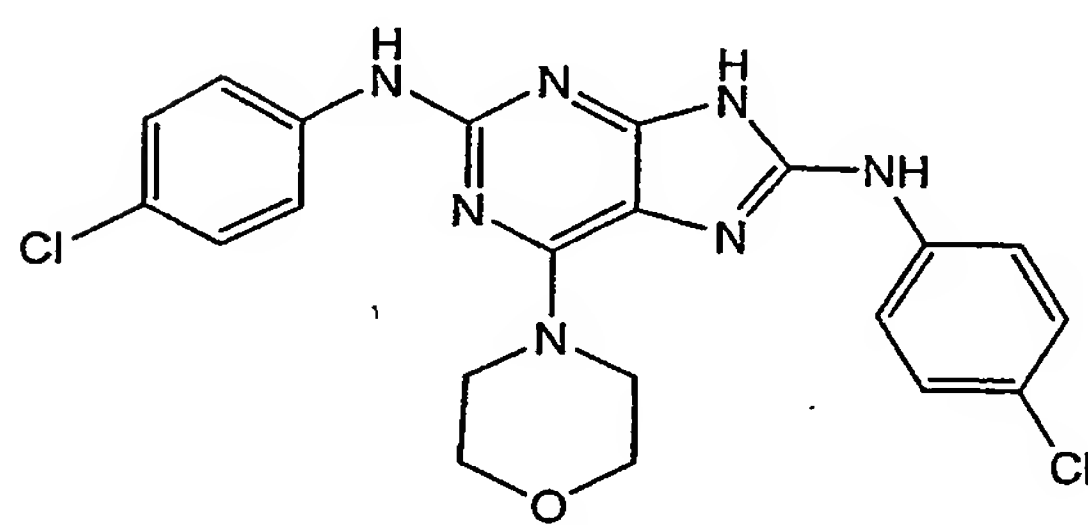
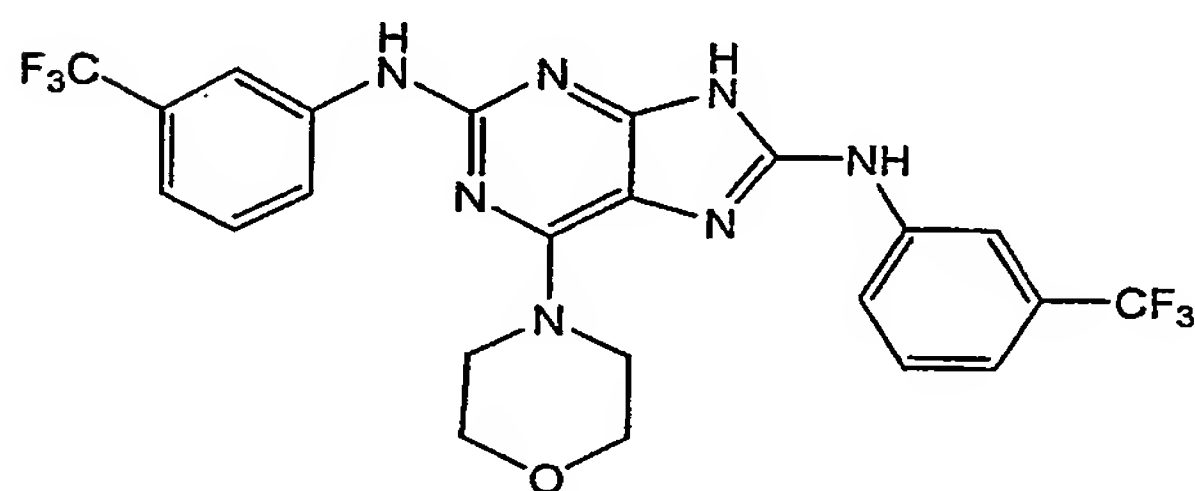
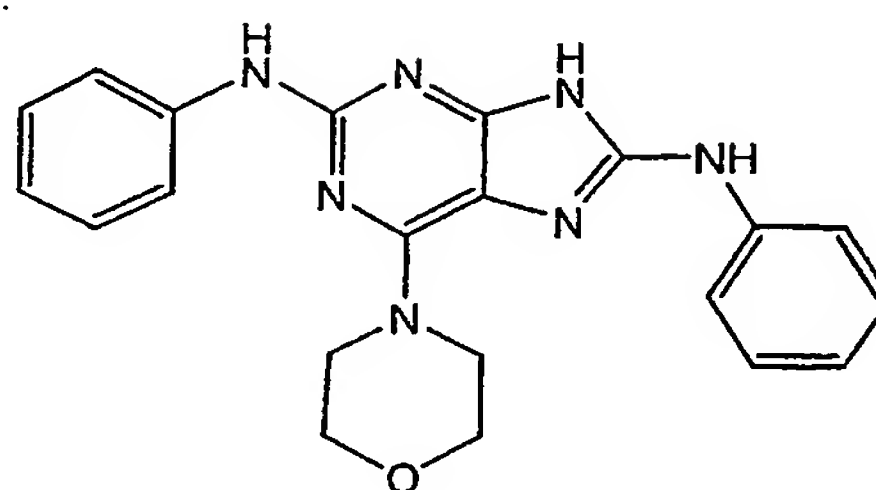
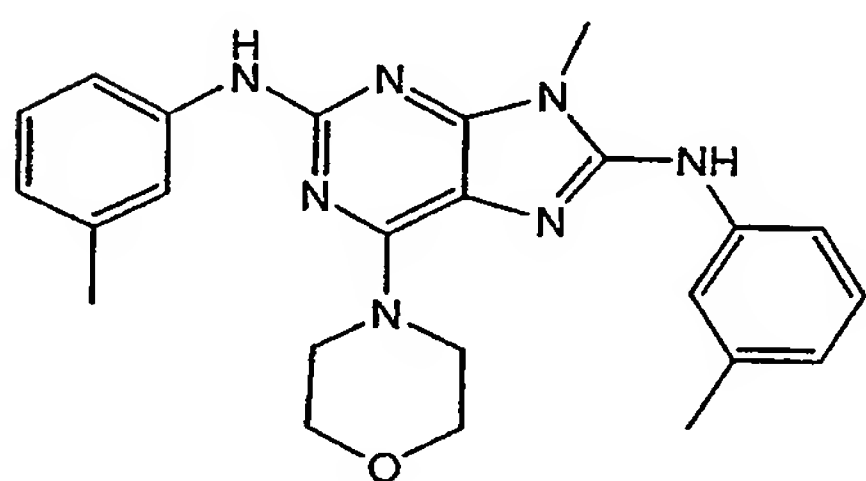
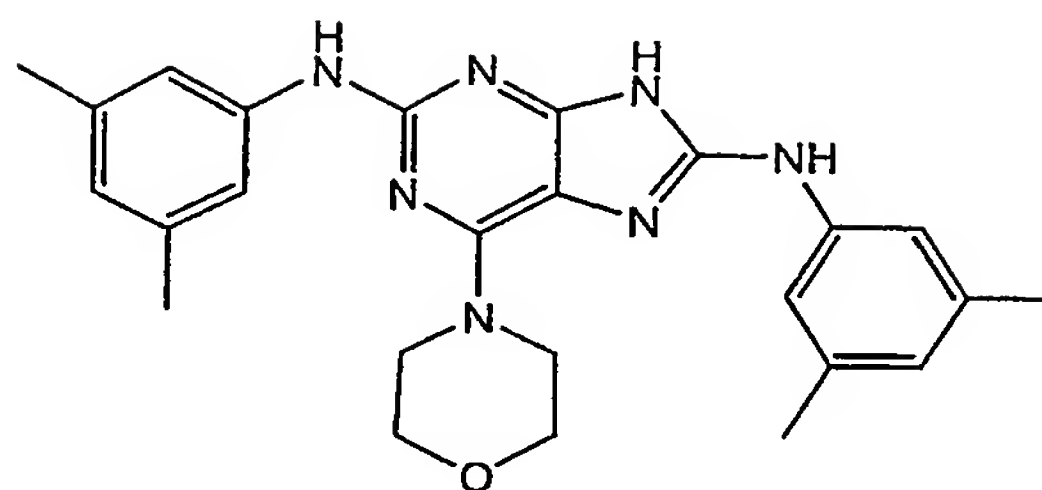
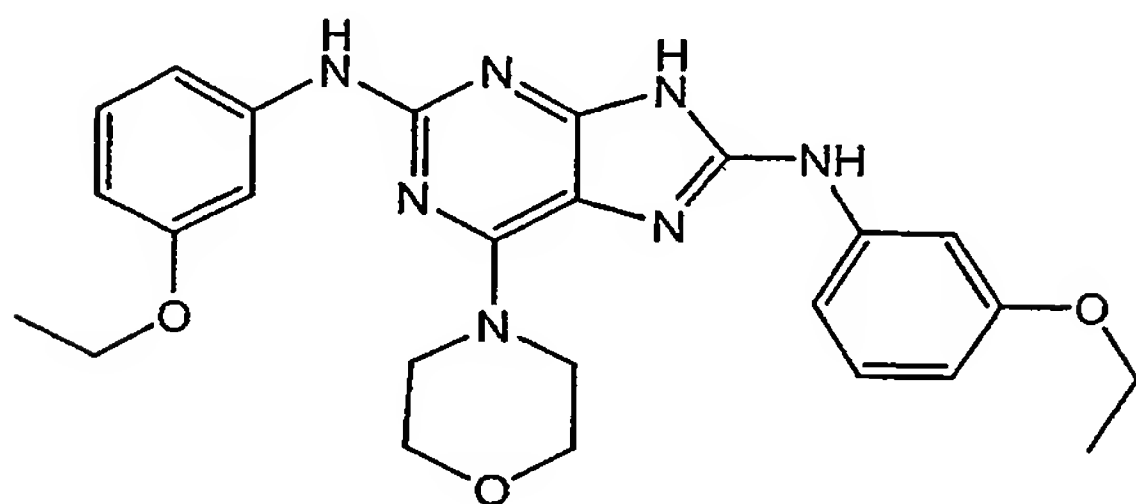
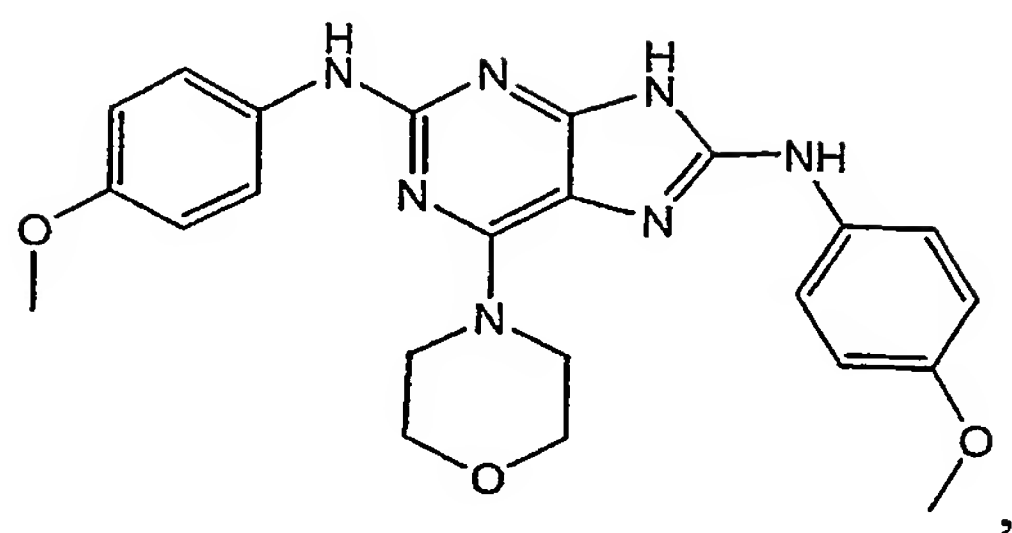
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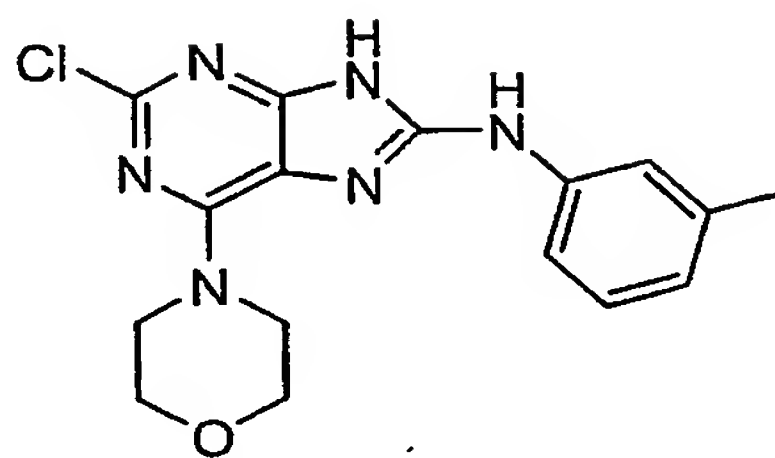
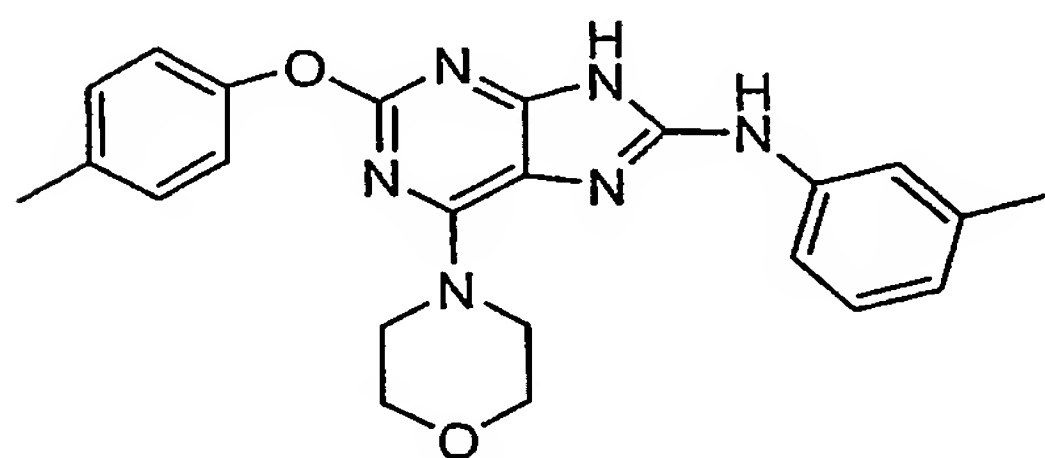
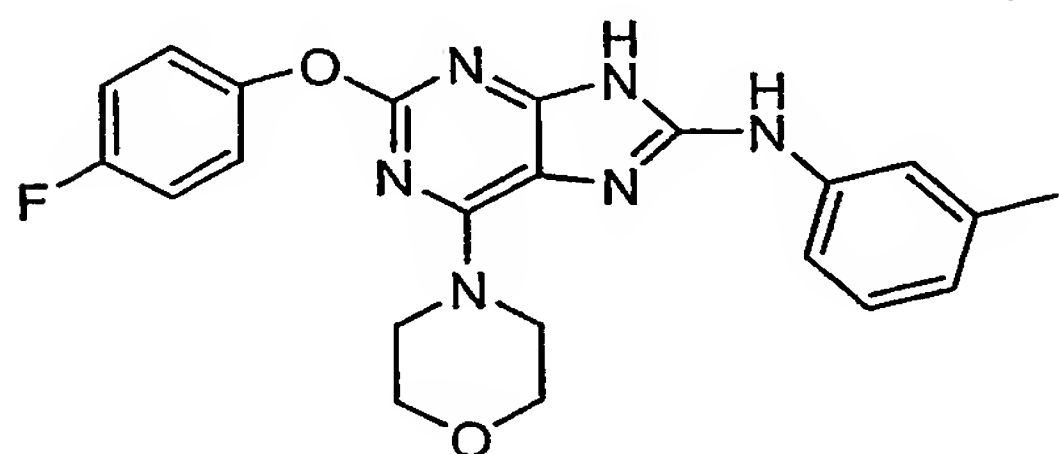
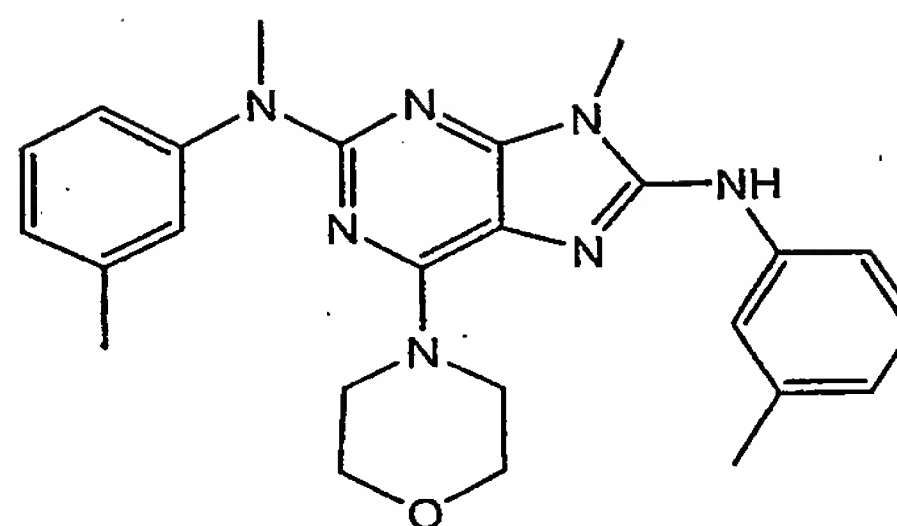
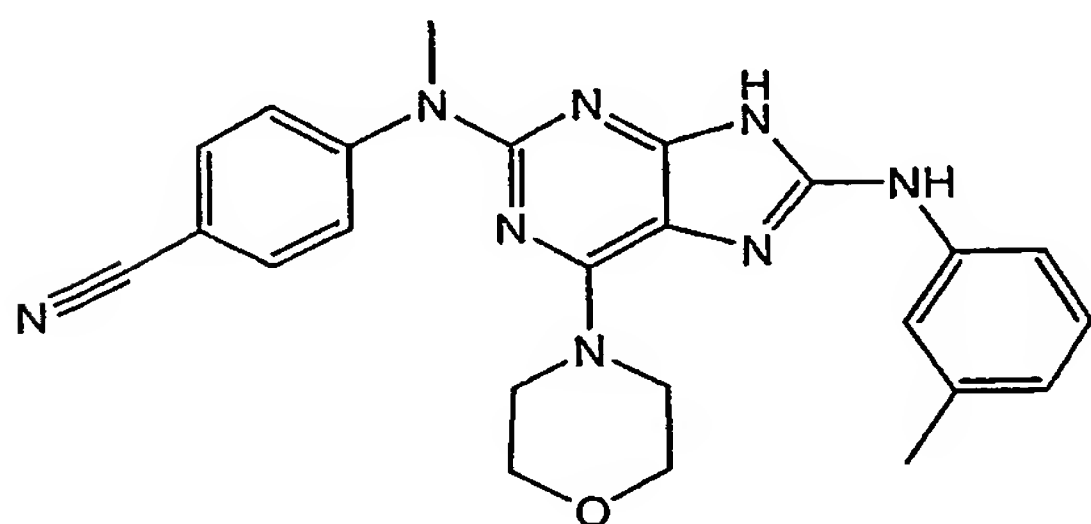
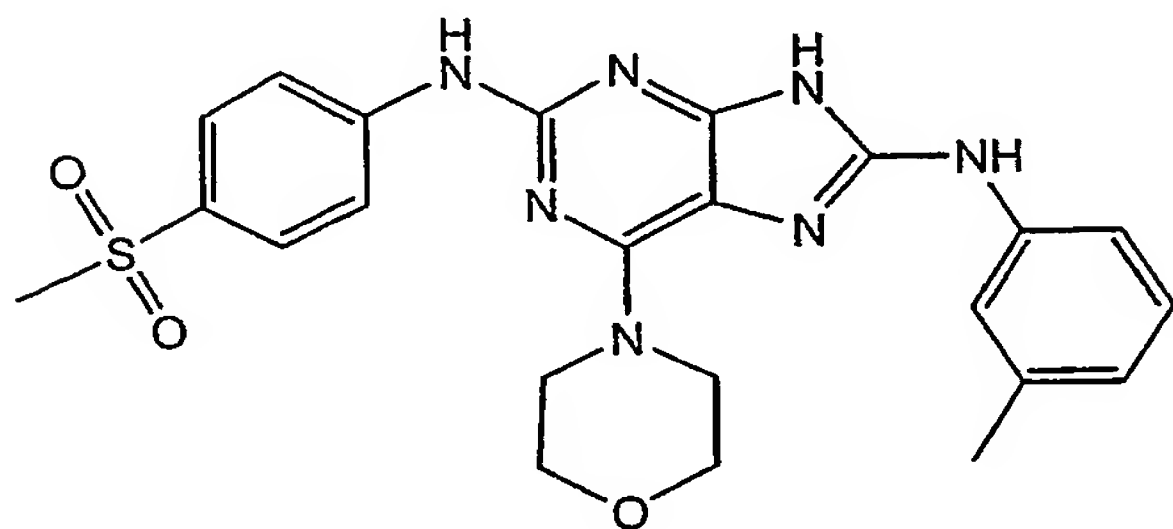
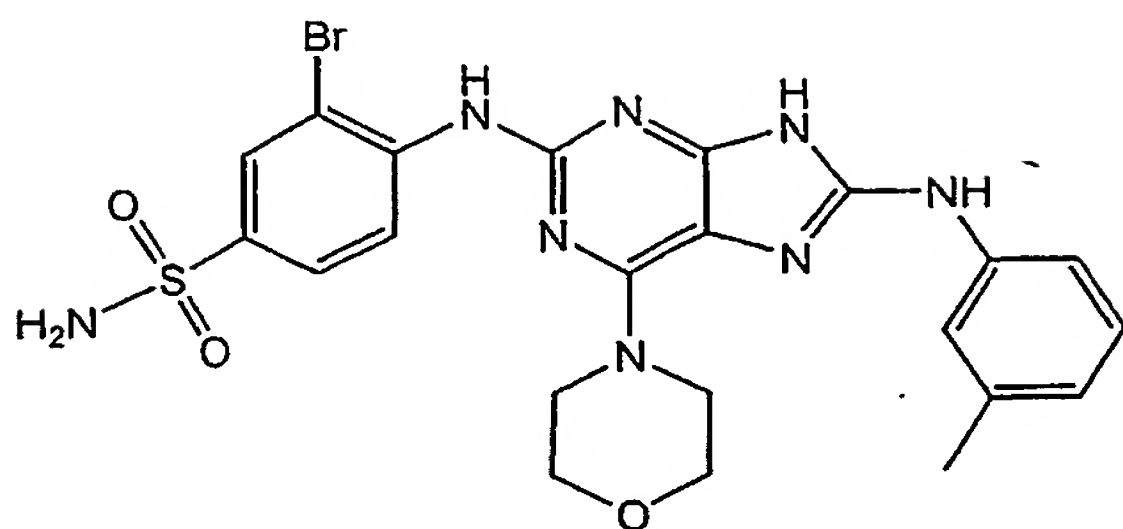


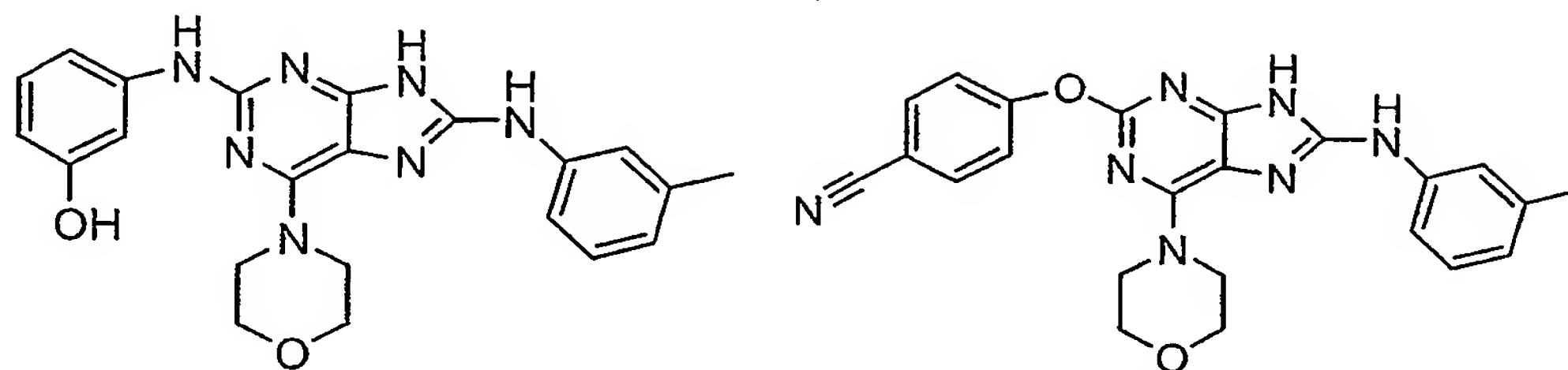




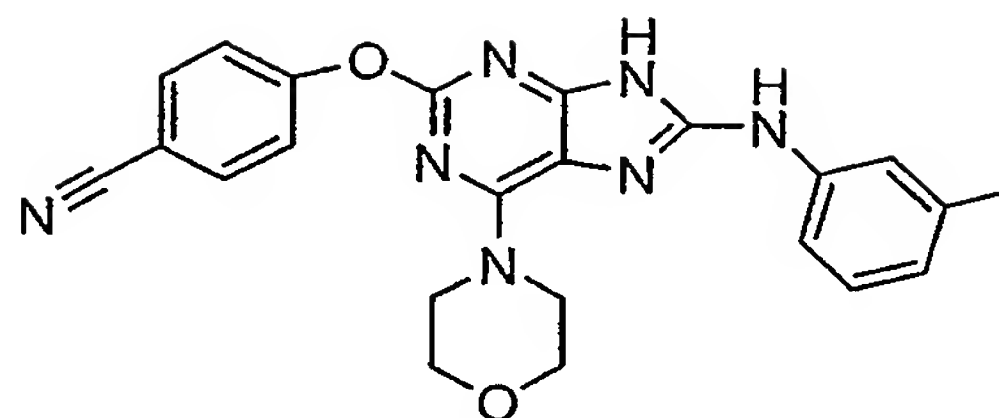




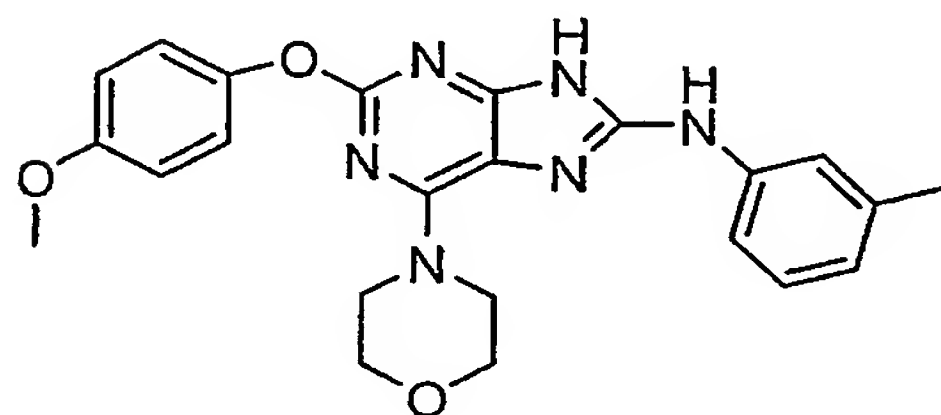




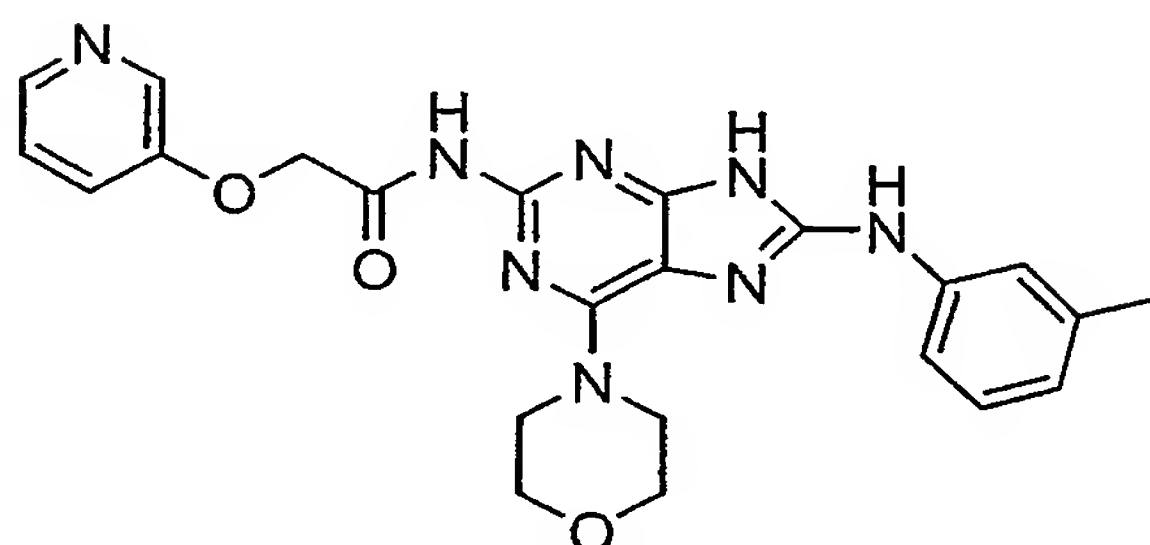
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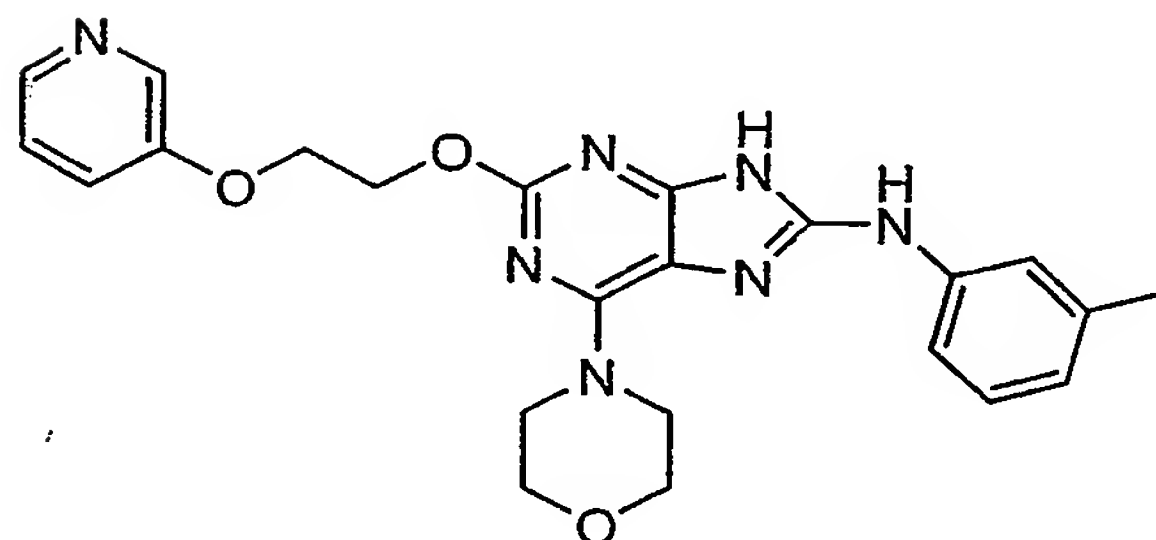
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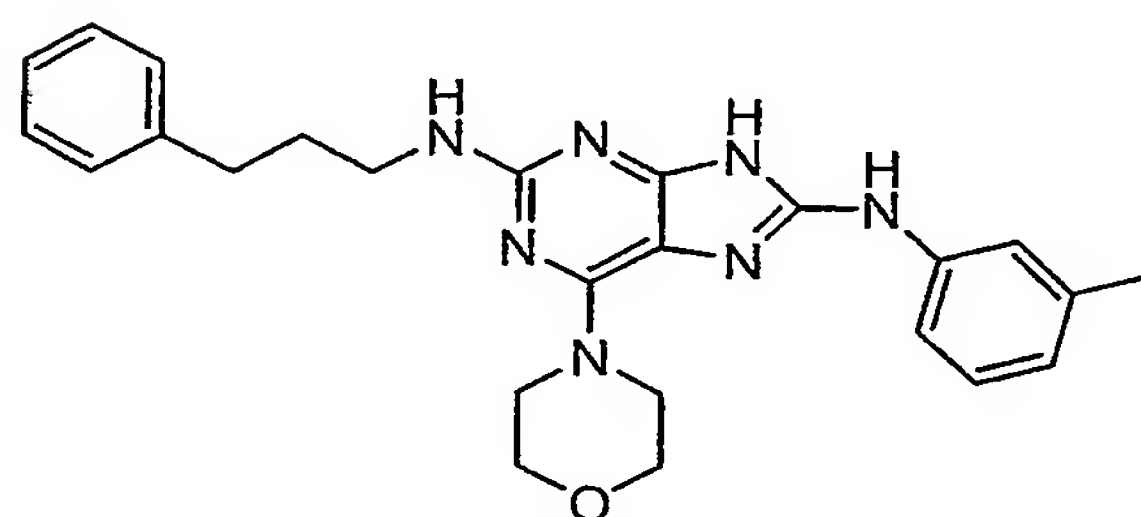
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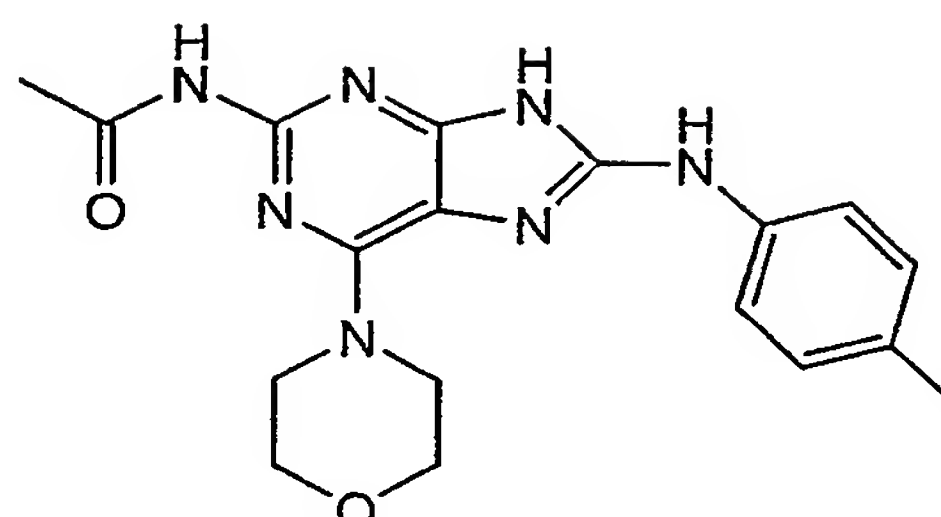
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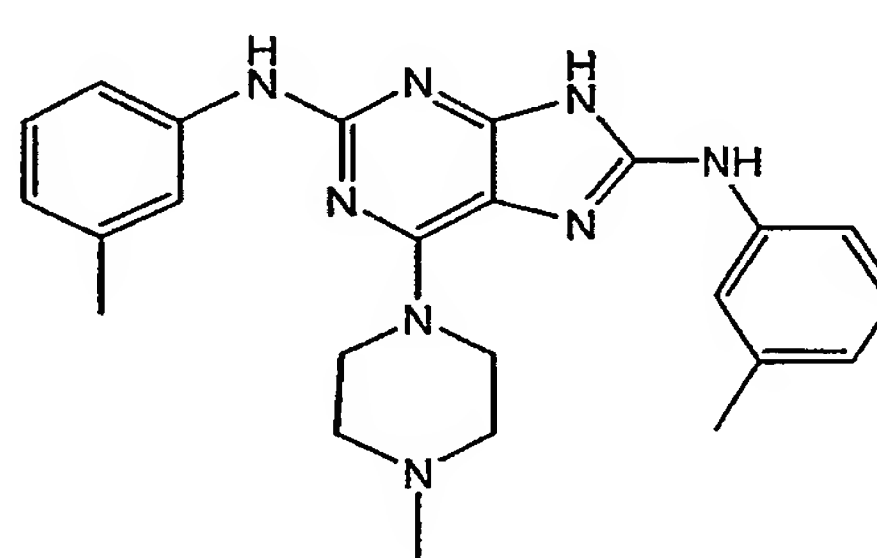
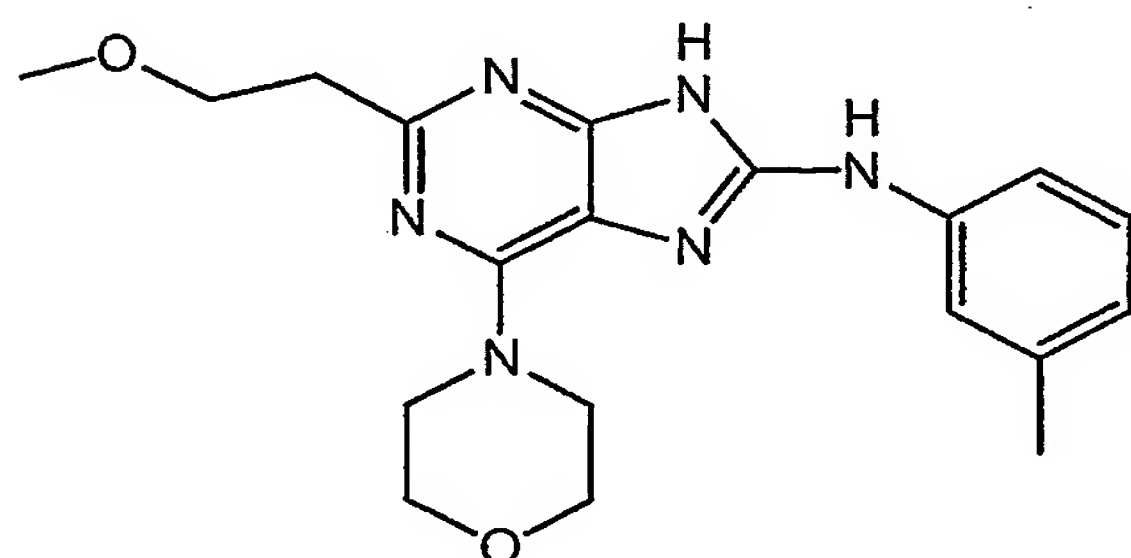
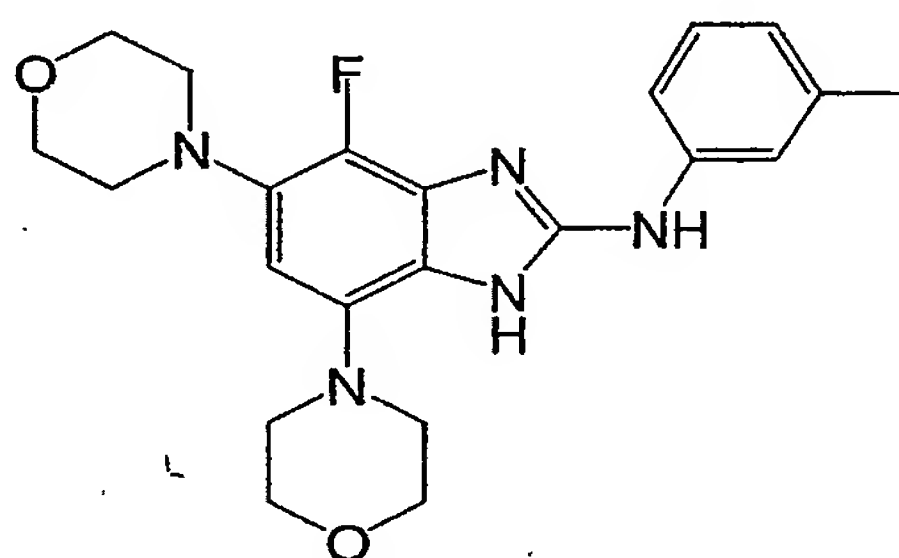
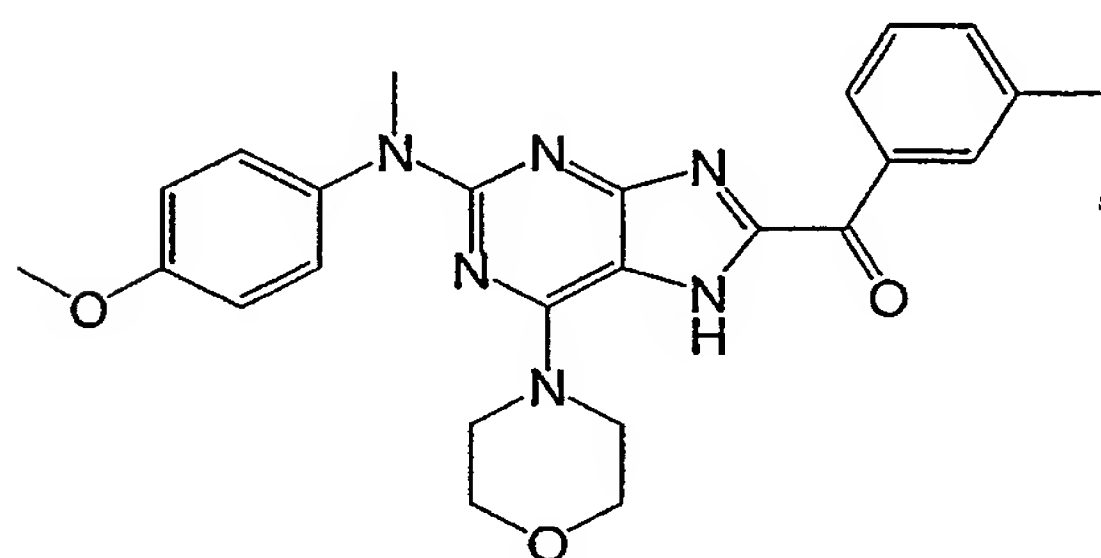
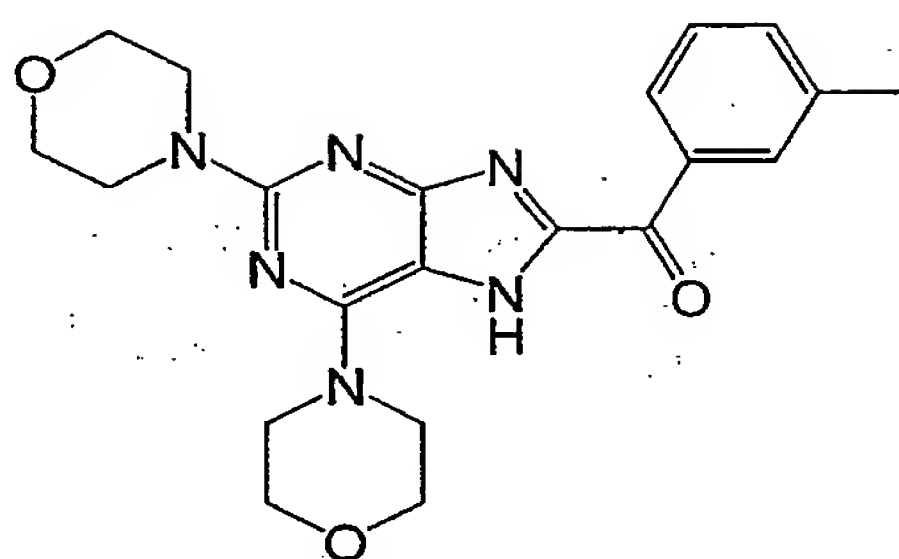
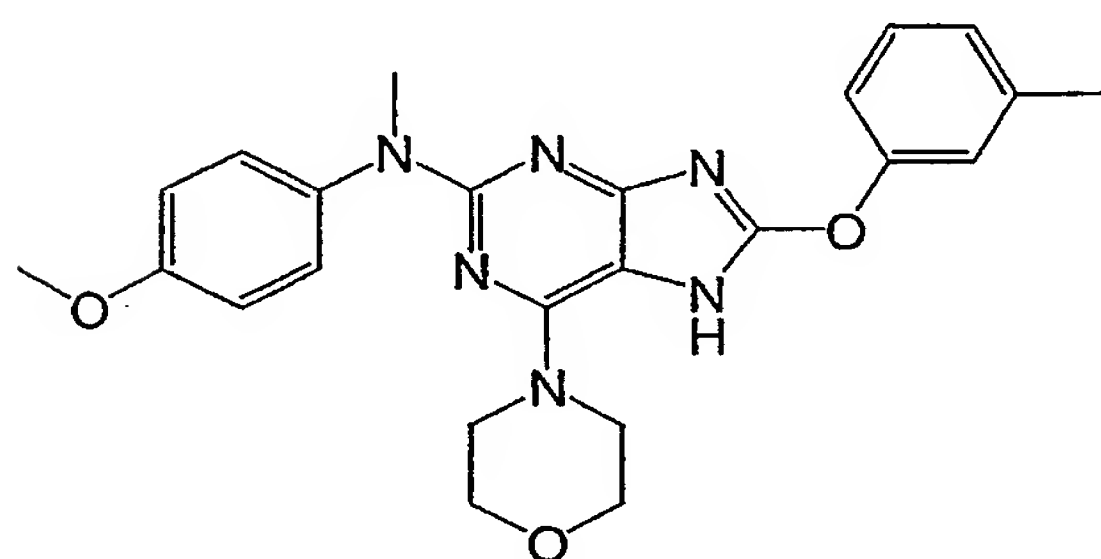
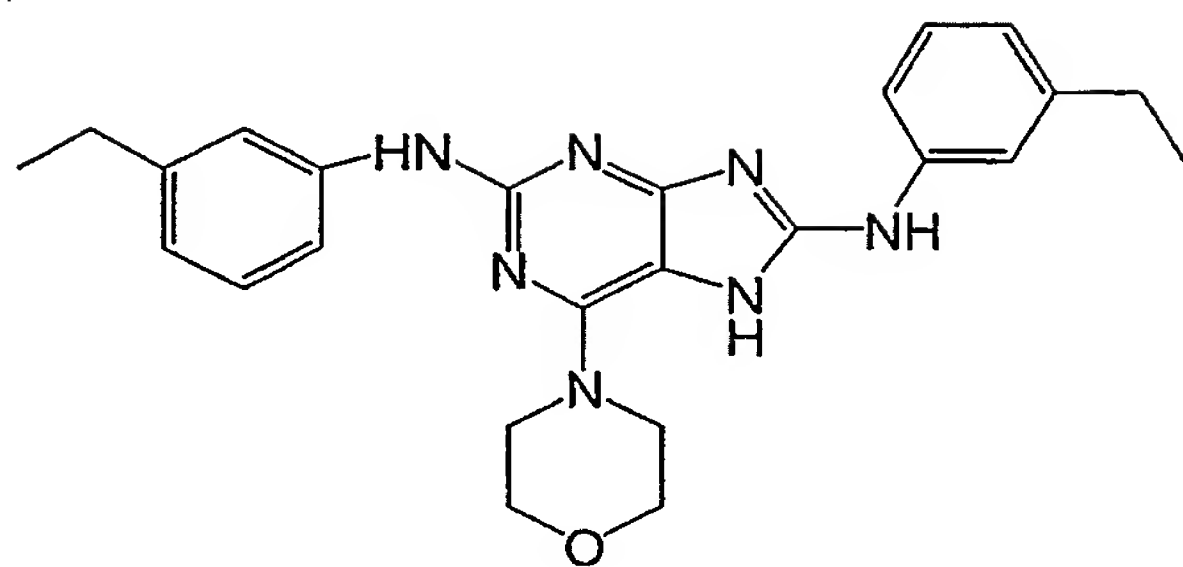
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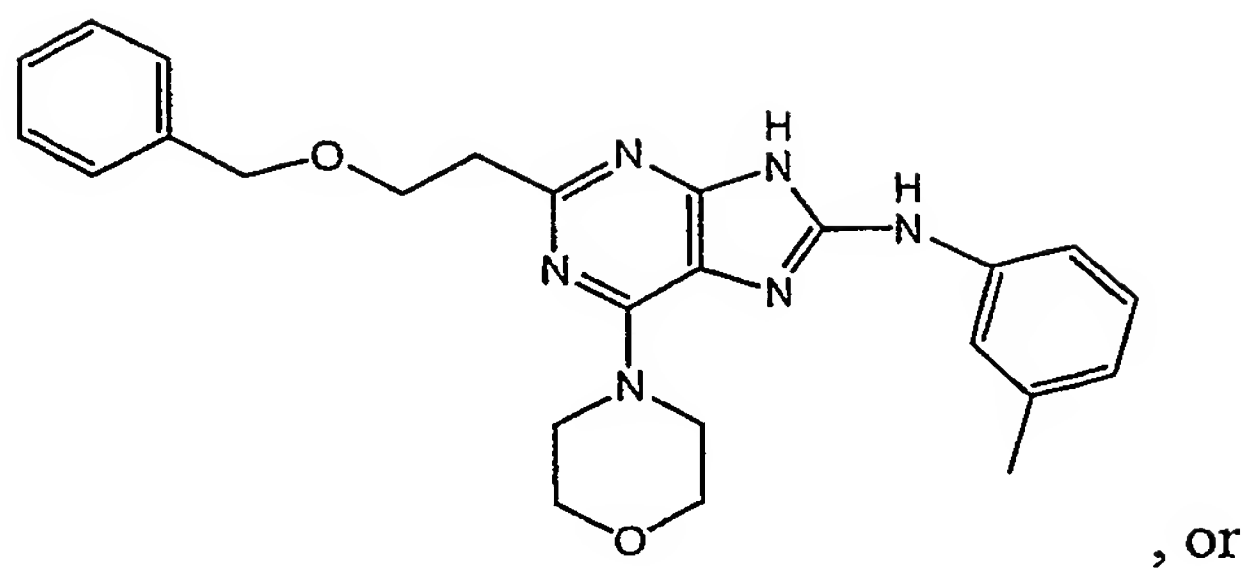


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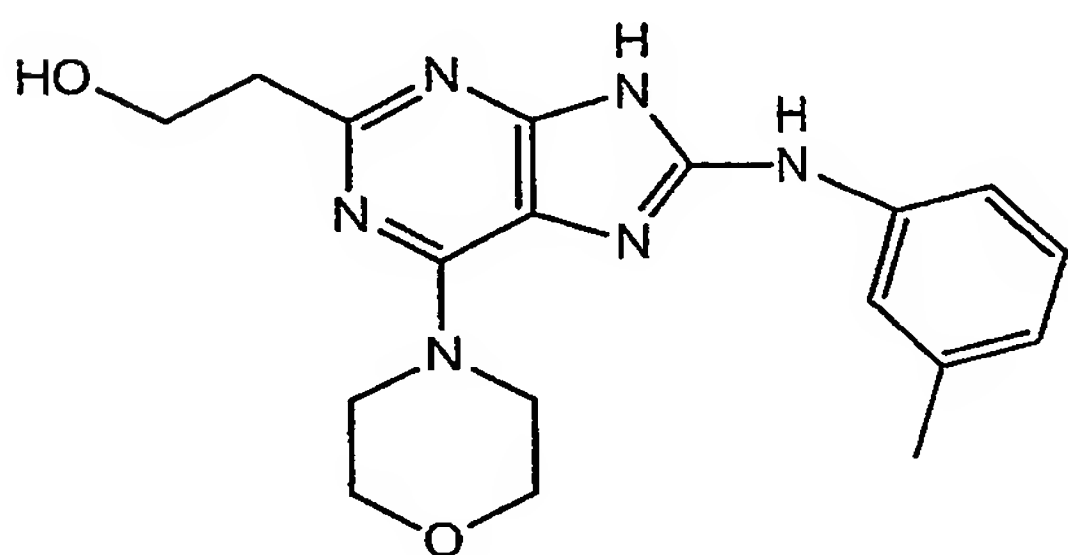


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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

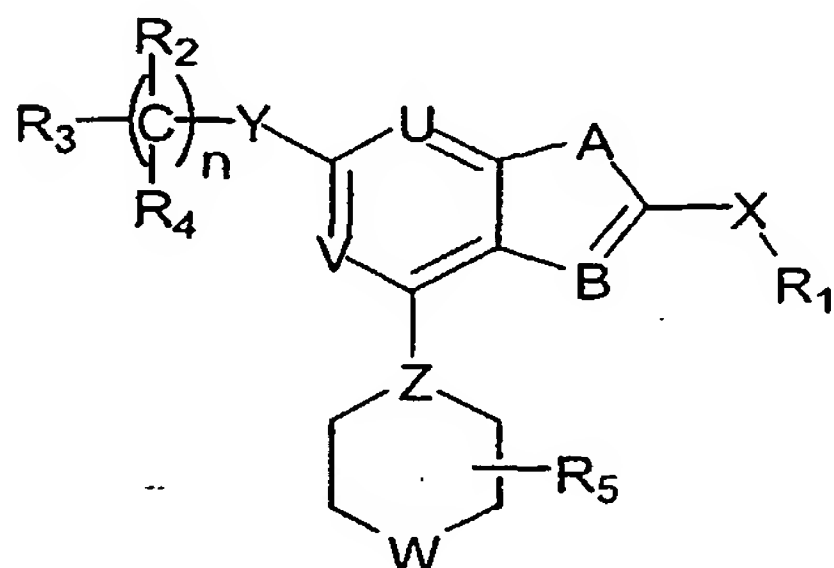
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: AROMATIC BICYCLIC HETEROCYCLES TO MODULATE IL - 12 PRODUCTION



(I)

(57) Abstract: This invention features a compound
of formula (I): R₁ is aryl or heteroaryl; each of R₂ and
R₄, independently, is H, halogen, CN, alkyl, OR^a, or
NR^aR^b; R₃ is H, halogen, CN, alkyl, alkenyl, alkynyl,
aryl, heteroaryl, cyclyl, heterocyclyl, OR^a, OC(O)R^a,
OC(O)NR^aR^b, NR^aR^b, NR^aC(O)R^b, NR^aS(O)R^b,
NR^aS(O)2R^b, NR^aC(O)NR^bR^c, NR^aC(S)NR^bR^c,
NR^aC(NR^b)NR^cR^d, NR^aC(O)OR^b, S(O)NTR^aRⁱ,
S(O)₂NR^bR^c, S(O)R^a, S(O)₂R^a, C(O)R^a, C(O)OR^a,
or C(O)NR^aRⁱ; R⁵ is H or alkyl; n is 0, 1, 2, 3, 4, 5,
or 6; A is O, S, S(O), S(O)₂, or NW; B is N or CR^c;
X is O, S, S(O), S(O)₂, NR, or C(O); Y is a covalent

bond, C(O), C=NR^a, O, S, S(O), S(O)₂, or NW; Z is N or CH; each of U and V, independently, is N or CR; and W is O, S, or NRⁱ; in
which each of R^a, R^b, R^c, and R^d, independently, is H, alkyl, aryl, heteroaryl, cyclyl, or heterocyclyl; R^e is H, alkyl, aryl, acyl, or
sulfonyl; and R^f is H, alkyl, aryl, acyl, sulfonyl, alkoxyl, amino, ester, amide, CN, or halogen. The compound is useful for treating
an interleukin- 12 overproduction-related disorder.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/32546

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61P 19/02,17/06,3/10,1/00;C07D487/04,471/04,498/04,513/04,401/10,405/10,407/10,409/10,413/10,417/10;
A61K 31/52, 31/522, 31/541,31/5355,31/4745,31/4743,31/496
US CL : 544/117,118,127,139,132,133,137,61,62,362,370,368,369,373;514/228.2,228.5,234.2,23

US CL : 544/117,118,127,139,132,133,137,61,62,362,370,368,369,373;514/228.2,228.5,234.2,234.5,233.8,233.5,
252.16,253.04,254.06,254.01,254.02,303,300,301,302,322,320,321,323,324;546/118,114,115,199,197,198,201
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : Please See Continuation Sheet

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,864,037 A (CHASIN et al.) 26 January 1999. See Abstract.	1-38
A	US 4,459,296 A (ANCHER et al.) 10 July 1984. See example 1	1-5, 25-30, 32-36, 38
A	US 4,946,843 A (JANSSENS et al.) 07 August 1990	1-5, 26-30, 32-36



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

09 July 2004 (09.07.2004)

Date of mailing of the international search report

02 NOV 2004

Name and mailing address of the ISA/US

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P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Mark L. Berch

Telephone No. 571-272-0663

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/32546

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: Please See Continuation Sheet
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/32546

Continuation of Item 4 of the first sheet:

Title not descriptive. New Title.

Aromatic bicyclic heterocycles to modulate 1L - 12 production.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-6(part), 7, 8-10 (part), 11-24, 25-38 (part), drawn to U=N V=N A=N B=N.

Group II, claim(s) 1 (part), 3-5 (part), 6 (part), 8-10 (part), 26 (part), 28-30 (part), 31 (part) 32 (part) 34-37 (part), drawn to U=N V=N A=O B=N.

Group III, claim(s) 1 (part) 3-5 (part), 6 (part), 8-10 (part), 26 (part), 28-30 (part), 31 (part), 32 (part) 34-37 (part), drawn to U=N V=N A=S B=N.

Group IV, claim(s) 1 (part), 3-5 (part), 6 (part), 8-10 (part), 26 (part), 28-30 (part), 31 (part), 32 (part), 34-37 (part), drawn to U=N V=N A=N B=C.

Group V, claim(s) 1 (part), 3-5 (part), 6 (part), 8-10 (part), 26 (part), 28-30 (part), 31 (part), 32 (part), 34-37 (part), drawn to U=N V=N A=O B=C.

Group VI, claim(s) 1(part), 3-5 (part), 6 (part), 8-10 (part), 26 (part), 28-30 (part), 31 (part), 32 (part), 34-37 (part), drawn to U=N V=N A=S B=C.

Group VII, claim(s) 1-5 (part), 26-30 (part), 32-36 (part), drawn to one of U, V=C, other=N, A=N B=N.

Group VIII, claim(s) 1(part), 3-5 (part), 26 (part), 28-30 (part), 32(part), 34-36 (part) drawn to U, V=C, other=N, A=O B=N.

Group IX, claim(s) 1 (part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to one of U, V=C, other=N, A=S B=N.

Group X, claim(s) 1(part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to one of U, V=C, other=N A=N B=C.

Group X I, claim(s) 1(part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part) drawn to one of U, V=C, other=N A=O B=C.

Group X II, claim(s) 1(part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part) drawn to one of U, V=C, other=N, A=S B=C.

Group X III, claim(s) 1-5 (part), 25-30 (part), 32-36 (part), 38 (part), drawn to U=C V=C A=N B=N.

Group X IV, claim(s) 1 (part), 3-5 (part) 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to U=C V=C A=O B=N.

Group X V, claim(s) 1 (part), 3-5 (part), 26(part), 28-30 (part), 32 (part), 34-36 (part), drawn to U=C V=C A=S B=N.

Group X VI, claim(s) 1 (part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to U=C V=C A=N B=C.

Group X VII, claim(s) 1 (part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to U=C V=C A=O B=C.

Group X VIII, claim(s) 1 (part), 3-5 (part), 26 (part), 28-30 (part), 32 (part), 34-36 (part), drawn to U=C V=C A=S B=C.

The inventions listed as Groups I - X VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: each group has its own special technical feature in the heterocyclic core to which the 2-3 substituents are attached. These 18 cores are, respectively, purine,

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/32546

oxazolopyrimidine, thiazolopyrimidine, pyrrolopyrimidine, faranopyrimidine, thienopyrimidine, imidazopyridine, oxazolopyridine, thiazolopyridine, pyrrolopyridine, furanopyridine, thienopyridine, benzimidazole, benzoxazole, benzothiazole, indole, benzofuran and benzothiophene. The core is essential for the utility, since the substituents themselves, e.g. morpholine or phenoxy do not themselves bond to receptors.

Continuation of Box II Item 3:

1(part), 2, 3-6 (part), 7, 8-10 (part), 11-24, 25-26 (part), 27, 28-32 (part), 33, 34-37 (part), 38

Continuation of B. FIELDS SEARCHED Item 1:

544/118, 127, 139, 61, 62, 362, 370,
514/228.2, 228.5, 234.2, 252.16, 253.04, 254.06, 303, 322
546/118, 199

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